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EXTRAPERITONEAL COLOSTOMY OR ILEOSTOMY

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AFTER any abdominal operation there is a risk of intestinal obstruction occurring as a complication or sequel, but with certain procedures the hazard is apparently much increased. One of the most notorious operations in this respect is abdomino-perineal excision of the rectum, for it may be followed by adhesions not only to the wound in the anterior abdominal wall and to adjacent viscera, but also to the suture line in the pelvic peritoneum, and to the colostomy site. In addition a loop of small bowel may become ensnared in the lateral peritoneal space on the outer side of the colostomy, as was pointed out by Rankin (1927) and Gabriel (1928). These authors have recommended that this paracolostomy space should always be closed by a purse-string suture at the original operation as a prophylactic measure to obviate this risk. That this step is effective in reducing the incidence of lateral space obstructions seems to be established by the follow-up report of Goligher, Lloyd-Davies, and Robertson (1951) on 1302 patients treated by combined excision of the rectum at St. Mark's Hospital between 1936 and 1949. In 170 cases the lateral space had not been closed and 3 of these subsequently developed obstructions in this space; by contrast in the 1132 cases in which the space was closed as a routine there were no examples of paracolostomy obstruction.

It would be reasonable to suppose that patients subjected to ileostomy and colectomy or proctocolectomy might also be specially predisposed to post-operative intestinal obstruction. Several writers have, in fact, testified to the frequency in these cases of a mechanical intestinal obstruction—not to be confused with that relatively more common obstructive condition of the ileostomy itself, the *ileostomy dysfunction* of Warren and McKittrick (1951). Thus Cattell (1953) recorded a late mortality of some 3 per cent from such obstructions in the ileostomy cases at the Lahey Clinic, Boston. Goligher (1954) stated that in a series of 74 patients treated by primary colectomy at St. Mark's Hospital, 4 developed post-operative intestinal obstruction, and Brooke (1956) encountered 11 early and late mechanical obstructions in his series of 130 patients treated by ileostomy and colectomy. Most of the recorded obstructions have been due to adhesions to the anterior or posterior abdominal walls or pelvic floor, but a number have arisen in connexion with the ileostomy; and Hardy, Brooke, and Hawkins (1949) and Goligher (1954) have pointed to strangulation of a loop of small gut in the para-ileostomy gutter as one of the possible mechanisms in this situation. They recommend that this gutter should always be closed at the time of the initial operation in the same way as the lateral space is obliterated in cases with an iliac colostomy.

For several years now it has been my invariable practice in fashioning a colostomy or ileostomy to close the lateral space by a purse-string suture, access to the space being obtained through the main paramedian wound as described in previous papers (Goligher, Lloyd-Davies, and Robertson, 1951; Goligher, 1954). In placing this suture care has always been exercised not to penetrate the bowel wall itself but only to take a bite of the peritoneal leaf of the mesocolon extending on to it. A non-absorbable suture material, usually linen thread, has been used, for some earlier experiences suggested that catgut could not be relied upon to secure a permanent obliteration of the space (Goligher, Lloyd-Davies, and Robertson, 1951). Since adopting this technique I have encountered no examples of lateral space obstruction in my own personal cases, and I was perfectly satisfied with the method till about eighteen months ago, when in 3 successive very ill patients with colitis treated by primary proctocolectomy and ileostomy, sepsis occurred around the purse-string suture, and persisted for several weeks till the stitch was finally extruded or extracted. Subsequent scarring and contraction then led to considerable indrawing of the outer edge of the ileostomy and the surrounding skin which made the fitting of an adherent ileostomy bag difficult and unsatisfactory.

After these experiences I turned my mind to devising an alternative technique for eliminating the paracolostomy, or para-ileostomy, space without having to resort to a non-absorbable suture of this kind. It occurred to me that a neat way of doing so would be to avoid creating a lateral space at all by bringing the ileal or colonic stump forwards, not across the peritoneal cavity, but *through the extraperitoneal tissues round the outer edge of the peritoneum.* This is usually an easy manœuvre, which when completed leaves the right or left half of the abdominal cavity, as the case may be, with a very smooth, relatively unruckled, peritoneal investment devoid

of foraminæ or fossæ. It may be that other surgeons have used a similar plan, but I have been unable to discover any account of it in the literature* and I think the method has certain advantages that warrant its description. The detailed technique will be described first of all for ileostomy and then for colostomy.

TECHNIQUE FOR ILEOSTOMY

It is presumed that the ileostomy is being performed at the conclusion of a colectomy or proctocolectomy and that the ileal stump to be used for forming the stoma is closed by a de Martel or Cope clamp. The first step consists of making a separate disk wound for the ileostomy. This is established with its centre usually about 3 in. to the right of the umbilicus and in the waist line To avoid traversing the deeper layers of the parietes in an unnatural position because of the relaxation of the peritoneum and abdominal muscles resulting from the open paramedian wound, the peritoneum, posterior and anterior rectus sheaths, and subcutaneous tissues or skin are caught with forceps and rendered taut by being drawn strongly to the left (*Fig.* 114). The ileostomy wound overlies the outer part of the rectus muscle and its sheath. The fibres of the anterior sheath are cut in cruciate fashion; the rectus muscle fibres are then similarly divided, exposing the posterior rectus sheath (*Fig.* 115, 1 and 2). This is also incised vertically and transversely, but with great delicacy so as *not to penetrate the closely adherent parietal peritoneum*, which is gently separated by scissor dissection from the aponeurosis at the outer angle of the wound (*Fig.* 115, 3 and 4). This blunt dissection is continued in an outward and backward direction to form a tunnel in the extraperitoneal tissues, which gradually turns the corner of the lateral edge of the peritoneal cavity.

The ileostomy wound is now forsaken temporarily and the right edge of the main paramedian wound is retracted strongly by the assistant, giving the surgeon who is standing on the left-hand side of the patient a clear view of the inside of the right half of the abdomen. It is also an advantage, though not essential, to tilt the patient 20 degrees to the left to tip the loops of small gut into the left abdomen. The cut edge of the posterior parietal peritoneum, forming the outer border of the raw surface created by the removal of the cæcum and ascending colon, is caught with long artery forceps roughly opposite the ileostomy stab wound (*Fig.* 116). With blunt dissection by scissors, and later by the index finger, a space is formed in the retroperitoneal tissues extending laterally and forwards to connect with the other tunnel that had been begun at the ileostomy wound (*Fig.* 117). A passage is now available for

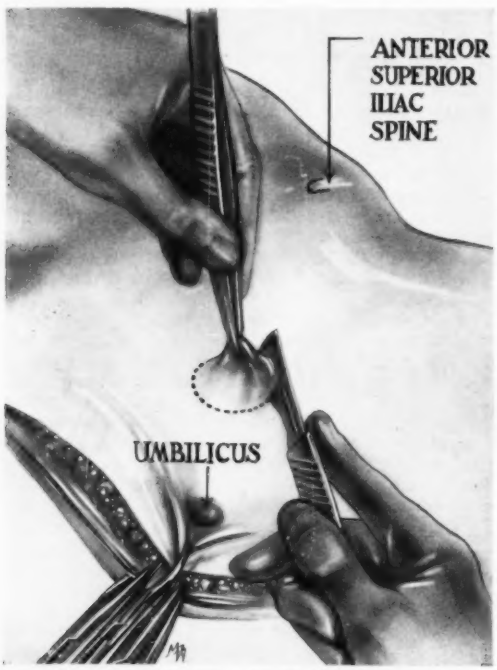

FIG. 114.—Making separate wound for ileostomy. Surgeon standing on left side of patient. Removal of disk of skin and subcutaneous tissues at a point lateral to and just below the level of the umbilicus.

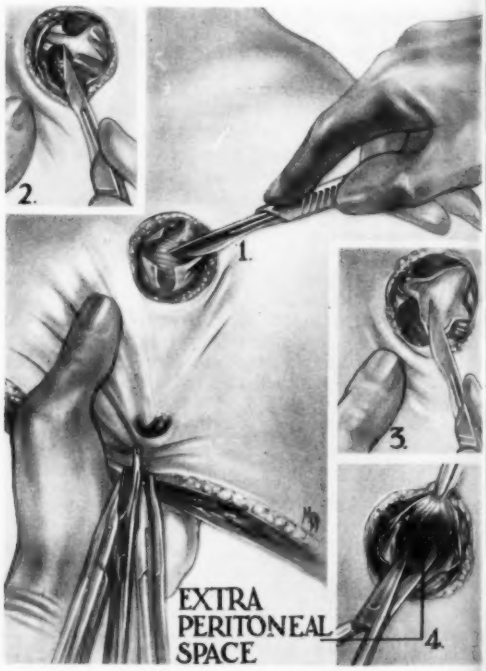

FIG. 115.—Making separate wound for ileostomy. Cruciate division of musculo-aponeurotic layers of abdominal wall: (1) anterior rectus sheath, (2) outer part of right rectus muscle, and (3) posterior rectus sheath. The peritoneum is not opened but instead an extraperitoneal tunnel is fashioned at the outer margin of the wound as in (4).

* Since this paper was submitted for publication a note on Extraperitoneal Colostomy has been published by C. P. Sames in the *Lancet*, 1958, I, 567.

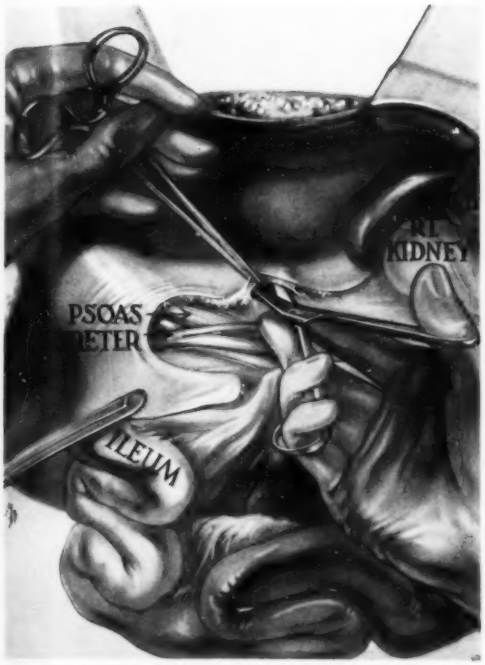

FIG. 116.—Beginning of inner end of extraperitoneal tunnel. View obtained by surgeon, standing on the left side of the abdomen, of the right half of the abdominal cavity at the completion of the colectomy. Peritoneal leaf at the outer edge of the raw area corresponding to the ascending colon being elevated and extraperitoneal space opened up.

FIG. 117.—Completion of extraperitoneal tunnel. Fingers of left hand being passed along tunnel from its inner end to meet those of right hand inserted through the outer end.

FIG. 118.—Drawing ileal stump and mesentery through the extraperitoneal space to emerge at the separate ileostomy wound.

FIG. 119.—Suture of outer leaf of peritoneum in turn to inner leaf of peritoneum to right colon, to ileal mesentery, and to ileum.

transmission of the ileal stump and its mesentery from the retroperitoneal tissues to the stab wound without transversing the peritoneal cavity. Before drawing the end of small gut through to the exterior in this way its mesentery is divided as required to provide a fairly free length of bowel, about 6 in. or 8 in. long, with an adequate blood-supply. The Cope's clamp on the end of the ileum is then threaded through the tunnel dragging the ileum and its mesentery after it (*Fig.* 118).

Some $2\frac{1}{2}$–3 in. of ileum will now project beyond the skin of the anterior abdominal wall when the stump is drawn taut. As far as possible it is fixed

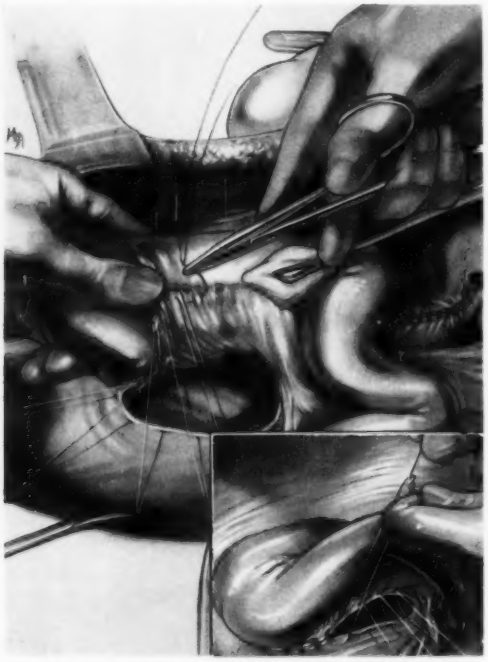

FIG. 120.—Suture of deep aspect of ileal mesentery (or of ileum itself) to the inner leaf of peritoneum. Care must be taken to catch only the peritoneal covering of the mesentery and not the underlying vessels, or, if the bowel is sutured, not to enter the bowel lumen but to insert the sutures as true Lembert stitches. *Inset*: Sutures tied.

in this position by 4–6 sutures of No. 2/0 chromic catgut on a fine atraumatic Kelly needle uniting the aponeurosis of the anterior rectus sheath to the peritoneum of the ileal mesentery but not to the ileal wall.

Re-peritonealization of the raw areas on the posterior wall of the right abdomen is now effected. A running stitch of No. 1/0 chromic catgut on an atraumatic Kelly needle is begun between the upper part of the cut edge of peritoneum of the right paracolic cutter and that overlying the outer border of the second part of the duodenum. As this stitch is continued downwards it brings the lateral peritoneal leaf into apposition in turn with the cut edge of the medial leaf of peritoneum of the hepatic flexure and ascending colon, with the upper part of the cut edge of the ileal mesentery, and finally with the front of that portion of mesentery going to supply the ileal stump. It finishes just short of the mesenteric border of the ileum itself (*Fig.* 119).

A small raw area usually shows below the loop of small bowel that is proceeding towards the retroperitoneal space to form the ileostomy, and can be closed by bringing the peritoneal edges together from side to side with a few fine chromic catgut sutures. This appears to make the posterior parietal peritoneum fit very snugly round the last coil of ileum, as seen from the front, but if this coil and its

FIG. 121.—Beginning of inner end of extraperitoneal tunnel for left iliac colostomy. View obtained by surgeon, standing on the right side of patient, of the left half of the abdominal cavity. Outer leaf of pelvic peritoneum being elevated and extraperitoneal tissues opened up by scissor dissection. Position of separate colostomy wound indicated by circular dotted line.

mesentery are turned forward and to the right, it is seen that there is a further raw area behind (*Fig.* 120). This can only be satisfactorily closed by approximating the medial edge of peritoneum to the deep aspect of the ileal mesentery, and this is easily done with a continuous suture or series of interrupted stitches of fine catgut on an atraumatic Kelly needle, the utmost care being exercised to catch only the peritoneal leaf of the mesentery and not to injure the mesenteric vessels (*Fig.* 120, *inset*).

This completes the re-peritonealization of the right half of the abdomen. No attempt is made to cover the raw areas on the left side corresponding to the descending and iliac colon. The abdomen is closed in layers. When the main wound has been

FIG. 122.—Completion of extraperitoneal tunnel. Fingers being inserted from either end of the tunnel.

FIG. 123.—Iliac colon about to be threaded through the tunnel, the Zachary Cope clamp being guided into it by the finger passed from the external opening.

FIG. 124.—Iliac colon drawn to exterior through the extra-peritoneal tissues.

FIG. 125.—Completion of the re-peritonealization.

covered with a dressing and sealed off, the formation of the ileostomy is completed by removal of the de Martel clamp, by everting and turning back the terminal inch or so of ileum on itself, and by suturing the full thickness of the cut edge of the bowel to the skin edges by a series of interrupted fine silk sutures. An adherent ileostomy bag is then applied.

TECHNIQUE FOR COLOSTOMY

It is presumed that the actual excision of the rectum has been completed and that a short sigmoid stump, closed by a de Martel's or Cope's clamp, is available for making the colostomy. The pelvic peritoneum is still unsutured and the self-retaining abdominal retractor, used to hold the parietal wound open during the operation, has been removed.

The colostomy is best established at a separate wound situated just above the junction of the outer and middle thirds of the line connecting the anterior superior iliac spine and umbilicus. In the formation of this wound a similar technique is employed to that used in ileostomy cases, with excision of a disk of skin and subcutaneous fat and cruciate division of the musculo-aponeurotic layers of the abdominal wall down to the anterior parietal peritoneum. The colostomy wound, however, being placed farther laterally, does not penetrate the rectus but only the oblique and transverse muscles. The peritoneum is not opened, but instead a tunnel is created by scissor dissection in the extraperitoneal tissues round its lateral edge to reach the space behind the posterior parietal peritoneum.

Attention is now turned to the main paramedian wound again, and its left side is retracted laterally, exposing the left leaf of the pelvic and iliac peritoneum. The edge of the leaf is caught with long artery forceps roughly opposite the site of the colostomy stab wound, and with a mixture of scissor and finger dissection a tunnel is created in the retroperitoneal tissues which connects with that started at the colostomy wound (*Fig.* 121). This tunnel is gently stretched throughout its length so that it will be able to accommodate the colon without constriction (*Fig.* 122). The colon stump, closed by the Cope's clamp, is then threaded through the tunnel to emerge at the stab wound (*Fig.* 123). If the length of the stump was correctly judged there should now be about 2 in. of colon projecting beyond the abdominal skin when the bowel is drawn comfortably taut (*Fig.* 124). Two or three catgut sutures are inserted in the aponeurosis of the external oblique in the stab wound and tied so as to include appendices epiploicæ or other portions of fat on the bowel. This fixes the colon securely in position without having to insert sutures actually in its wall

The pelvic peritoneum is now sutured with continuous No. 1/0 chromic catgut on a fine Kelly needle. As the stitch proceeds from in front backwards and upwards the apposition of the peritoneal flaps becomes progressively more difficult until finally a point is reached (usually about 1½–2 in. below the main inferior mesenteric ligature) above which it is impossible to bring them further together. The stitch so far will have drawn the left flap as a hood over the iliac colon and mesocolon, as they tunnel to the left in the extraperitoneal tissues. The re-peritonealization of the posterior abdominal wall in the region of the aortic bifurcation is completed by stitching the obliquely-running upper part of the edge of the left leaf of peritoneum to the front of the iliac mesocolon and colon, and the vertically running edge of the upper part of the right flap to the free border of the iliac mesocolon (*Fig.* 125).

The abdomen is now closed and dressings applied to the main wound. A towel or pack is placed over these, and the fashioning of the colostomy is completed. The Cope's clamp is removed and the end of the bowel opened up. Using fine serum proof black silk sutures on straight cutting needles the distal edge of the colon is approximated to the edge of the circular skin wound, the bowel being slightly turned back on itself in the process. Finally a 'Vaseline' gauze or dry gauze dressing is applied.

DISCUSSION

The extraperitoneal technique has now been used for the establishment of a colostomy in 45 cases and of an ileostomy in 14. As a rule it has been easily executed, its performance in ileostomy cases being further facilitated by special attention to two points: (1) In the process of excising the right colon, the colic vessels and medial leaf of peritoneum running to it are divided *as close as possible to the bowel.* This conserves a larger peritoneal flap on the inner side, which renders the re-peritonealization of the right posterior abdominal wall somewhat easier. (2) During the process of making the extraperitoneal passage for the ileal stump, it is an advantage if the dissection is not confined simply to the creation of a narrow tunnel, but is extended to mobilize the lateral peritoneal flap widely so that it stretches farther medially and drapes itself more easily and smoothly over the ileum and its mesentery.

So far no drawbacks have been discovered in the method. Its advantages are that it completely eliminates the lateral space with its potentialities for obstruction, and also avoids the sharp ledge formed by either the iliac colon and mesocolon with a colostomy, or the ileum and ileal mesentery with an ileostomy, made by orthodox techniques. Goligher, Lloyd-Davies, and Robertson (1951) have pointed out that even when the lateral space had been closed in colostomy cases obstruction might still arise due to a loop of small gut becoming adherent to the edge of iliac mesocolon as it crosses the peritoneal cavity to reach the colostomy stab wound. With this extraperitoneal technique the stump of iliac colon and mesocolon or ileum and ileal mesentery is entirely covered by peritoneum as it runs forwards to the anterior abdominal wall, so that the risk of small bowel becoming stuck to it ought to be obviated.

It appeared that there might be two other possible advantages of the extraperitoneal technique. It is well known that however much care is lavished on the detailed technique of a colostomy operation, and however snugly the abdominal wall is made to fit round the bowel, a subsequent incisional hernia is practically inevitable. With the extraperitoneal technique just described the colon escapes obliquely from the peritoneal cavity, through what might be regarded as a valvular opening, and it seemed reasonable to suppose that this might less readily allow the egress of abdominal contents through the colostomy wound alongside the colon. It was also

conceivable that after an ileostomy made by this technique the terminal ileum might be better fixed by its passage through the extraperitoneal tissues than it would be after ileostomy fashioned by orthodox transperitoneal methods, and it was therefore hoped that ileostomy prolapse or recession might turn out to be less common with this new technique, not that they are common complications as it is. All the patients who have been given extraperitoneal colostomies or ileostomies have been operated on during the past eighteen months, and many of them very recently, so that clearly sufficient time has not yet elapsed to afford them a full opportunity to develop such sequelæ. But already two or three of the colostomy cases show some slight pericolostomic bulging, and one of the ileostomy cases has developed some degree of recession of her ileostomy bud on recumbency, so that it begins to appear doubtful whether the extraperitoneal technique will have special merits in this connexion.

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IMPLANTATION METASTASES FROM CANCER OF THE LARGE BOWEL*

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FROM the published work of Goligher, Dukes, and Bussey (1951), Cole (1952), Vink (1954), Naunton Morgan (1957), and others, it is now proved that metastases occur by implantation of cells derived from the primary growth by desquamation into the lumen of the bowel. Implantation may occur on to any raw surface in the bowel below the growth, or at the anus, or at the suture line following restorative resection unless adequate measures, such as those recommended by Goligher, Dukes, and Bussey, are taken to prevent it. Probably, however, carcinoma cells are also shed from the peritoneal surface of a bowel cancer and give rise to the widespread peritoneal deposits seen in late cases and possibly to implantation metastases in scars, such as occurred in the case described below.

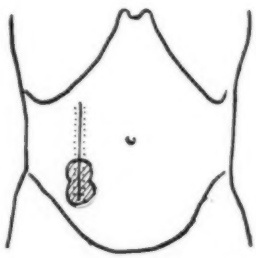

FIG. 126.—Diagram of the implantation metastasis as it first presented in *Case* 1.

Case 1.—In September, 1954, at St. Mark's Hospital, a right hemicolectomy was performed on an obese man of 61 years for carcinoma of the cæcum. The growth was 2½ in. in diameter, partially obstructing the ileum, and puckering the peritoneum over the cæcum. It was not fixed, however, and there were no metastases elsewhere in the peritoneum or in the liver. A radical removal of the terminal ileum and right colon was obtained with a good margin of the related mesenteries. An end-to-end anastomosis of terminal ileum to transverse colon was made and the patient's immediate recovery was uneventful. The growth was reported by Dr. Dukes to be a colloid carcinoma of average grade malignancy with glands involved up to the point of ligature.

The patient was readmitted to St. Mark's Hospital on the first anniversary of his operation, complaining of a pain and a lump in the operation scar. He had lost weight and was again anæmic, but there had been no vomiting or distension or any disturbance of his regular bowel habit. On examination there was a hard lump 2 in. × 1½ in. in the muscles of the abdominal wall beneath the lower end of the right paramedian scar (*Fig.* 126). The lump was a little tender and became more prominent when the abdominal muscles were contracted, but the skin was free to move over it. The possibility of an inflammatory origin for the lump was considered, but from every point of view it seemed likely to be a metastatic deposit in the scar, and this became certain when the lump remained hard and continued to grow rapidly in size during the next ten days. No biopsy was taken, but the patient was referred to Mr. Ivor Williams at St. Bartholomew's Hospital, who agreed with the diagnosis and gave a course of high-voltage radiation. The lump decreased in size for a time but the patient died with numerous metastases five months later.

It seems possible that this metastasis arose from a fragment of carcinoma implanted into the wound at the time of operation, and it is the purpose of this paper to examine the frequency with which such implantation metastases occur, the precise manner of implantation, and to suggest means for their prevention.

In an earlier paper (Boreham, 1956) I have shown that implantation metastases occur in the scars of open operations on the bladder for carcinoma in about 10 per cent of cases, and that in 5 per cent such a metastasis was the first sign of recurrence. Recurrences are also known to occur in scars following operations for carcinoma of the larynx,

* The work for this paper was carried out at the Middlesex, St. Mark's, and the Whittington Hospitals, where the author held Senior Registrar appointments.

bronchus, stomach, kidney, and breast, where the wound may come into contact with the outer surface of the growth and receive an implant of a few malignant cells.

If metastases occur in operation scars by implantation of cells from the peritoneal surface of a bowel cancer, one would expect them to be seen with some frequency around the colostomy following perineo-abdominal excision of the rectum. In this operation, after the perineal dissection and abdominal

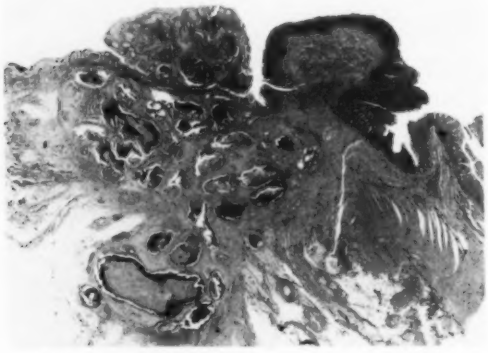

FIG. 127.—Section across the mucocutaneous junction of the colostomy of *Case* 3, showing the metastasis lying between the skin on the left and colonic mucosa on the right.

mobilization of the rectum are complete, it is usual to lead the specimen, with its lower end tied into a glove, out through a small wound in the left iliac fossa, before dividing the bowel above the growth to make the terminal colostomy. During this manœuvre, the whole outer surface of the excised bowel containing the growth is wiped over the edges of the colostomy wound, and any loose carcinoma cells present may be left in the wound. No contamination of the wound by cells from the lumen of the bowel can occur, however, unless the rectum has been wounded during its removal.

The following previously unpublished cases from St. Mark's Hospital illustrate metastases possibly arising by implantation in this way.

Case 2.—Male, aged 50. Perineo-abdominal excision by Mr. W. B. Gabriel for carcinoma of the rectum, October 2, 1947. There was a growth in the upper third of the rectum, of low-grade malignancy, with glands invaded, but not up to the point of ligature of the inferior mesenteric artery. The growth was invading the rectal wall with moderate invasion of perirectal fat. In November, 1951, there was an indurated mass at the lower margin of the colostomy. In June, 1952, the mass was larger and biopsy showed a recurrent adenocarcinoma of low-grade malignancy. Liver metastases were now present. The patient died in March, 1953.

Case 3.—Perineo-abdominal excision of the rectum for carcinoma by Mr. L. E. C. Norbury, 1945. The growth was found to be arising in the sigmoid colon which was folded over into the front of the rectum and was adherent to it by extension of growth. These adhesions were disturbed to allow delivery of the growth through the colostomy wound. Eighteen months later there was a recurrence at the colostomy and it was treated by excision. Section of this specimen is shown in *Fig.* 127. There is a focus of low-grade adenocarcinoma in the scar, separated from the bowel mucosa by a fissure.

It is another slight advantage of the synchronous combined technique that such recurrences around the colostomy cannot occur, the rectum being removed through the perineum.

I have records of 5 other cases of recurrences around a colostomy, but in 2 of them the growth was very extensive locally and the excision was not considered by the surgeon at the time to be a radical one; 2 others followed a Paul-Mikulicz type of resection where the possibility of contamination of the wound by bowel contents cannot be excluded; and 1 other had four carcinomas of the rectum associated with familial polyposis coli, so that the tumour developing later at the colostomy was very likely another primary carcinoma. I have also collected a number of cases of recurrences in the perineum following excision of the rectum for carcinoma, but I can find no case where the recurrence could not have arisen owing to incomplete excision of local spread in the first place; so that none of them can be attributed to implantation from this source with any assurance. But I think that some perineal recurrences occur by implantation of cancer cells from the lumen of the bowel into the wound when spill is allowed to occur, either by accidentally opening the rectum during the course of the excision or by incomplete occlusion of the anus.

Searching clinical and out-patient records for further implantation metastases in abdominal scars I found only 7 other cases with tumours in scar tissue and 2 of these proved to be non-malignant.

Case 4.—A woman of 62 attended the Middlesex Hospital in February, 1955, complaining of pain and tenderness in a scar in the right iliac fossa with attacks of colic and loss of weight. She had had an operation elsewhere for appendicitis in 1951. On examination there was a hard nodule half an inch in diameter just above the appendicectomy scar and barium enema showed a large filling defect in the cæcum suggestive of carcinoma. It was thought possible that the nodule had arisen by implantation from the carcinoma of the cæcum present at the time of appendicectomy. Biopsy of the nodule, however, showed chronic inflammatory tissue and fibrosis around a piece of ligature material.

Case 5.—A man of 53 had a restorative resection for carcinoma of the rectosigmoid region performed by Mr. Naunton Morgan at St. Mark's Hospital in November, 1954. In April, 1955, there were two nodules in the scar which were increasing in size and only slightly tender, and the wound was explored. The nodules were found to consist of dense fibrous tissue with calcification, and the absence of any recurrent growth was confirmed on section.

Case 6.—A woman of 62 had a right hemicolectomy for carcinoma of the ascending colon performed by Mr. D. K. Mulvany in June, 1954. Six months later there was a small lump immediately beneath the scar and on exploration a further recurrence was found in the retroperitoneal tissues. Both were excised and section confirmed the presence of adenocarcinoma.

Case 7.—A woman of 42 was seen at St. Mark's Hospital in January, 1956, complaining of a tender lump in an abdominal scar following an operation at another hospital in 1951. On examination there was an indurated and puckered area half an inch in diameter in the right paramedian scar. It was thought to be an inflammatory lesion and the affected part of the scar was excised and

the wound resutured. Section showed a recurrence of adenocarcinoma in the scar. Inquiry from the other hospital revealed the following information: A laparotomy and transverse colostomy were performed in February, 1951, for peritonitis due to perforation of the colon at the site of a growth in the sigmoid. The bowel was also obstructed at this site. The growth was resected after a stormy recovery from the first operation and proved to be an adenocarcinoma of average grade.

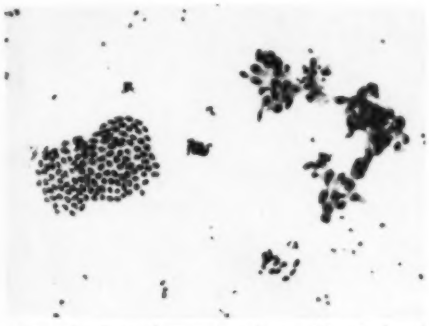

FIG. 128.—Smear from peritoneal coat of bowel where it was puckered by a carcinoma, showing desquamated peritoneal cells but no malignant cells.

There seems little doubt that in this case bowel contents containing carcinoma cells were spilled into the peritoneal cavity owing to a spontaneous perforation and that an implantation metastasis subsequently grew in the scar. There were probably other metastases arising in the same way in the peritoneal cavity, but the long interval before the implant in the skin brought the patient for further advice is unusual even for a low-grade tumour.

Another case illustrates this mode of implantation :—

Case 8.—A man of 69 was admitted to St. Mark's Hospital in November, 1952. He had had intestinal obstruction in the previous August when a carcinoma of the rectum had been found and a transverse colostomy made. A month later the abdomen was again explored, but the growth was found to be adherent to the bladder and was deemed irremovable.

On Dec. 1, 1952, Mr. Naunton Morgan explored the abdomen and found it possible to mobilize the rectum containing the growth and to do a restorative resection. The usual routine of using 1-500 perchloride of mercury to wash out the rectum below a clamp at the lower level of division of the bowel was carried out, and the bowel divided below the clamp to prevent implantation metastases at the suture line (Goligher, Dukes, and Bussey, 1951). During removal, however, the clamp slipped and there was gross contamination of the wound with bowel contents. The growth was found on section to be of low grade with little local spread, the adhesions being inflammatory in nature. Mesenteric glands were involved, but not up to the point of ligature. The colostomy was later closed and the patient made an uneventful recovery.

In August, 1955, however, he developed a small nodule in the scar and biopsy from this showed a focus of adenocarcinoma. In August he was readmitted to St. Mark's Hospital with partial large-bowel obstruction due to a large recurrence of the growth in the pelvis ulcerating into the rectum. At a further laparotomy the growth was found to be filling the pelvis and there were numerous deposits studded all over the peritoneal cavity.

In this case I think that slipping of the lower clamp with contamination of the wound by bowel contents containing malignant cells caused implantation metastases in the pelvis, in the scar, and all over the peritoneal cavity.

Case 9.—A matron of a nursing home, aged 53, had a perineo-abdominal excision for carcinoma of the rectum by Mr. Naunton Morgan in November, 1937.

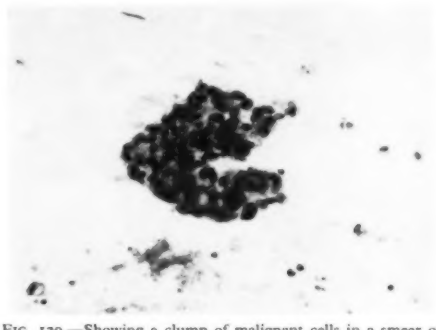

FIG. 129.—Showing a clump of malignant cells in a smear of the bowel content below a carcinoma.

The growth was large, situated in the middle third of the rectum, of average grade, and not penetrating the muscular coat of the bowel. There were no glandular or other distant metastases, but there were numerous adenomata in the bowel up to the point of division of the sigmoid colon.

Nineteen days later a second operation was required to relieve a small-bowel obstruction, which was found to be due to a loop of small bowel stuck between the layers of the mesentery of the portion of bowel forming the colostomy. Thereafter the patient remained well until November, 1938, when she was found to have a lump in the scar of the second laparotomy. It was the size of a shilling, hard, puckering the scar, and with one finger in the colostomy it could be felt to be in the abdominal wall. A barium enema was performed and showed no second primary carcinoma in the proximal colon, though there were numerous other polypi.

The lump grew steadily larger in spite of a course of irradiation and the patient died of her disease in the early part of 1940.

Case 10.—A lady of 67 was operated on by Mr. Paul Savage at the Whittington Hospital in November, 1956, when a large carcinoma of the colon was resected, together with the uterus and a portion of bladder to which it was adherent. There were no distant metastases and only one of the twenty-seven mesenteric glands was involved. Three months later the patient developed a lump 1 in. in diameter in the lower end of the scar, which proved on section to be a recurrence of the adenocarcinoma. It was excised and she remains free of further recurrence six months later.

Of the cases so far described, only in *Cases* 1, 2, 3, and 6, and possibly in *Cases* 9 and 10, does contamination of the wound by the peritoneal surface of the growth seem to have given rise to implantation metastases.

Further evidence of this mode of spread was sought for in three ways :—

1. Smears were taken on to a glass slide by rubbing the edge of it over the peritoneal surface of the specimen opposite the growth and especially

where the peritoneum was puckered. These smears were stained in various ways, mostly by Papanicolaou's method, and compared with smears similarly obtained from the peritoneal surface of the normal bowel, and with smears made of mucus from within the bowel and with paraffin sections of the primary tumour. Fifty-two specimens have been examined

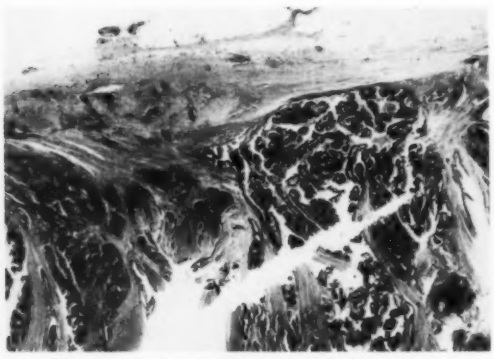

FIG. 130.—Section through the bowel wall at a site where it was puckered, showing the growth separated from the serous surface by subserous fat.

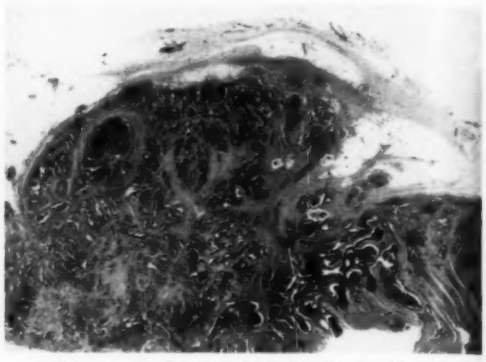

FIG. 131.—Section through the bowel wall with a piece of parietal peritoneum adherent to it, showing how the latter has protected the peritoneal cavity from the growth.

FIG. 132.—Section through the bowel wall opposite a site of peritoneal puckering, showing a layer of granulation tissue and fibrin protecting the growth.

in this way and, while the interpretation of the smears is not easy, I have been unable to detect any malignant cells in the smears taken from the serous coat of the bowel. There were clumps of cells in many of the smears (*Fig.* 128) which probably represent desquamated peritoneum and in some ways resemble malignant clumps, and these were found much more frequently in the smears taken from sites of peritoneal puckering. None of the clumps, however, contains cells with the characteristics of malignancy as described by Bader and Papanicolaou (1952), Warren H. Cole (1952), and others. In some of the smears obtained from within the lumen of the bowel, however, there are groups of cells which could have been shed from the tumour (*Fig.* 129). The frequency with which these cells are found and the distance they may reach from the tumour have been well shown by Warren H. Cole, who was one of the first surgeons to point out the significance of this finding and to use it to improve the technique of cancer surgery of the large bowel.

2. Sections have been cut across the full thickness of the bowel wall through any point of peritoneal puckering or apparent ulceration opposite the growth. In a consecutive series of 35 carcinomas of the large bowel arising above the peritoneal floor and examined by Dr. Morson in the pathological department at St. Mark's Hospital, 16 were found to show such puckering. These sections have been studied again with Dr. Morson, and in only 4 of them were malignant cells found ulcerating on to the peritoneal surface of the bowel. In two of these cases the growth had already spread across the peritoneal cavity and caused discrete peritoneal nodules, which were excised separately. A third had already spread to the left ureter, causing a hydronephrosis, and was reported by Mr. Henry Thompson (1952) to the proctological section of the Royal Society of Medicine; and the fourth was an anaplastic high-grade tumour of the ileocæcal region.

Thus, of these 35 cases one can say that there was no ulceration of tumour cells on to the puckered peritoneal surface of the bowel in any case where it seemed possible to do a radical operation.

In the other 12 cases where the peritoneum was puckered the extent of malignant invasion fell short of the serous coat of the bowel by a variable margin. In some cases (*Fig.* 130) the cells were protected from desquamation on to the surface of the growth by a layer of subserous fat, so that here, as in some other aspects of cancer surgery, fat may be the surgeon's friend.

In another case (*Fig.* 131) there was a piece of parietal peritoneum adherent to the serous coat of the bowel opposite the growth and preventing ulceration, but the growth had still not spread to the plane of separation between the two adherent serous surfaces.

In other cases (*Fig.* 132) there was a layer of granulation tissue between the advancing malignant cells and the peritoneal surface. It may be that this layer of granulation tissue represents part of the stroma of the tumour and that as the malignant

epithelial cells grow into it, it becomes incorporated in the growth as its connective tissue base. But it seems that, for some time at least, granulation tissue and fibrin proliferate on the peritoneal surface of the growth and prevent cancer cells from being shed into the peritoneal cavity or on to the wound or the surgeon's hands during operation.

Nevertheless, this protective layer of fibrin and granulation tissue may be no more than a few cells thick, it is fragile, and it eventually breaks down to

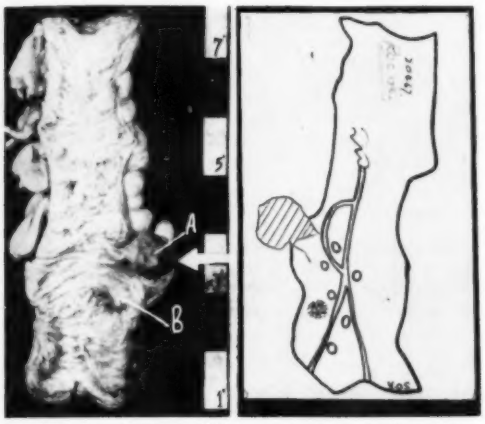

FIG. 133.—Specimen of *Case* 11, showing an implantation metastasis at the site of perforation of a diverticulum. A, Malignant polyp; B, Scar of perforated diverticulum containing an implant.

produce those peritoneal seedlings seen in late cases. It is impossible to tell by inspection of the bowel how easily cancer cells may be shed from the growth and sown in the wound or peritoneum in this way. Therefore it is advisable to handle the growth as little as possible, and when possible to cover the growth with a swab. Such a swab may be kept in place by tapes tied around the bowel as described by Cole (1952), but this requires two additional holes to be made through the mesocolon and might cause a troublesome hæmatoma or damage to lymphatic vessels which may contain growth. This can be avoided by incorporating a thin sheet of malleable metal in the swab, so that it can be moulded on to the growth by finger pressure.

I have experimented with various thicknesses of aluminium alloy and copper sheet for this purpose and have found that freshly annealed copper sheet was the most suitable. As supplied, the copper is stiff and springy, but it can be annealed by holding it over a gas flame until it reaches cherry-red heat (about 600° C.) and then plunging it into cold water. It then becomes easily malleable and can be moulded with the fingers on to the colon. This moulding, moreover, by a process known as 'work hardening' returns the copper to its stiff springy state and helps to retain it and the swab in the desired position. The annealing takes only a few moments and the copper then remains malleable for about twenty-four hours, or until 'worked'. The annealing is unaffected by temperatures involved in boiling or autoclaving. Aluminium requires to be annealed in a furnace. A copper sheet about 8 in. × 5 in. has been found most suitable, and is annealed as described and then wrapped in several layers of gauze, and sterilized by boiling or autoclaving. As a further precaution against implantation it may be moistened with perchloride of mercury 1–500 and then used to wrap around the colon, and will hold itself in position. This technique, however, is only suitable for growths in those parts of the colon which have a mesentery, and cannot easily be adapted for growths of the rectum.

3. It was my intention to perform a series of excisions using this technique and to compare the results with previous series as far as the incidence of recurrences in scar is concerned. But I have found so few recurrences in scars of excisions of large-bowel tumours, except where the growth was advanced or gross contamination of the wound with bowel contents occurred, that this has been abandoned and I have not used the technique as a routine. It could be used as an added safeguard, however, in those cases where it was felt that the growth was nearly through on to the serous coat of the bowel, but that there were as yet no distant metastases. I do not think that surgical implantation often occurs by shedding of malignant cells from the peritoneal surface of a growth at operation. *Cases* 7 and 8 and the following cases, however, illustrate how easily implantation occurs by contamination of wounds with bowel contents.

Case 11.—October, 1955. This lady was operated on by Mr. Henry Thompson on Jan. 15, 1955, for generalized peritonitis due to a perforated diverticulum of the sigmoid colon. The perforation was closed by suture and the peritoneum drained. Six months later a malignant polyp was found in the sigmoid colon and resected. Section (*Fig.* 133) shows a friable malignant polyp with no invasion of the stalk. One inch below the stalk is a raw area, section of which shows a piece of suture material buried in granulation tissue which is being invaded by carcinoma implanted thereon by the adjacent malignant polyp.

I also have detailed records of 8 cases of carcinoma of the large bowel with implantation metastases at the anus. One of these was a man who developed an adenocarcinomatous polyp at the anorectal ring after injection of hæmorrhoids in the presence of an unsuspected carcinoma of the colon. The histology of the primary and the implant was identical.

Another case developed an implant at the anorectal ring, having had a hæmorrhoidectomy in the presence of an undiagnosed carcinoma of the colon.

The other six all occurred in cases with a history of abscesses or long-standing fistulæ at the anus and were found to have adenocarcinomatous tissue in perianal granulations with a separate primary tumour of similar histology higher in the bowel. Four of the six had had multiple anal operations over a period of years before the implant occurred.

SUMMARY AND CONCLUSIONS

I am convinced, and I think I have shown conclusively, that carcinoma of the large bowel does give rise to implantation metastases. These occur readily on to raw surfaces in the bowel below a growth, especially fistulæ and wounds at the anus.

They also occur on to suture lines in the large bowel after resection of a growth unless precautions are taken to prevent this. Only one definite recurrence at the suture line by implantation has occurred at St. Mark's Hospital since the instigation of routine irrigation of the bowel with perchloride of mercury below an occluding clamp before division. In this one case the clamp slipped and there was gross contamination of the wound by bowel contents. Implantation rarely occurs from the peritoneal surface of the growth on to the abdominal wound, but some recurrences of growth around a colostomy or in the perineum may arise in this way. Possible ways of preventing this have been described.

I wish to express my sincere thanks to Mr. D. H. Patey, under whose sponsorship the work for this paper was started at the Institute for Clinical Research at the Middlesex Hospital. I am also very grateful to Dr. Cuthbert Dukes and Dr. Basil Morson, of St. Mark's Hospital, for much help and advice on pathological matters; and to Mr. Gabriel, Mr. Naunton Morgan, Mr. Lloyd Davies, and the surgeons at St. Mark's Hospital for their patient teaching and advice and for allowing me to report their cases. I am also grateful to Mr. Cecil Murray, of the Middlesex Hospital, Mr. Desmond Mulvany, and Mr. Paul Savage, for allowing me to report their cases, and to Mr. Bussey, of St. Mark's Hospital, and Mr. Moore, of the Whittington Hospital, for the photomicrographs.

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PRIMARY CARCINOMA MULTIPLEX

A SERIES OF 17 CASES WITH REVIEW OF THE LITERATURE

BY VERNON PENNELL, CAMBRIDGE

PRIMARY cancer occurring in more than one organ, or in more than one site in a single organ, is no rarity. Indeed by 1932 Warren and Gates had investigated or described 1259 cases. The most surprising fact is the rarity of British authors adorning the literature, and none in recent years has described a series of cases.*

It would appear that the idea of a unicentric origin of carcinoma is gradually giving place to the view that a multicentric origin is not uncommon, and that cancer, so far from being a local disease, is more of the nature of a general condition. It is this comparatively recent change of opinion which has prompted the publication of this, admittedly, short series of cases taken from the records of Addenbrooke's Hospital during the past five years.

The surgeon spends more time and trouble over the attempt to understand and eradicate the disease of carcinoma than any other condition of comparable gravity, and the fact that multiple primary disease is—or at least appears to be—on the increase should warn him of possible plurality and encourage him to redoubled efforts when this unhappy diagnosis is confirmed. A case such as that described (p. 110) by Maddock, Lipinsky, Lien, and Alt (1956) or *Case* 2 of this series, both of which patients remained happy and well, enjoying life after several operations, the former living nearly thirty years after her first operation, and the latter seventeen years (to date), offers some slight compensation to the profession of surgery, and perhaps some hope in apparently hopeless cases.

* Since the completion of this paper and before its publication Wallace has published a paper (*Brit. J. Surg.*, 1957, **45**, 165) on some 134 patients with more than one primary tumour, to which author acknowledgement is made.

HISTORICAL

To Billroth, whose passport to fame needs no scrutiny, must go the credit for the earliest publication of two cases in 1869, though it appears certain that one of these cases had been previously reported by him some nine years earlier. Perhaps, unfortunately, Billroth, with his passion for accuracy and meticulous attention to detail, laid down certain postulates to be fulfilled before the title of multiplicity could be legitimately conferred: namely, each growth to be of proven malignancy, to be separate and situated in a different organ, to have a different cytohistology, and to be devoid of any possibility of being a metastasis; furthermore, each growth must produce its own (and separate) metastases. Doubtless these almost prohibitive terms militated against publication (with its consequent addition to knowledge) and may account for the paucity of recordings until some twenty-five years later.

In 1932 Warren and Gates undertook the first compilation of series of cases and liberalized Billroth's all too narrow definitions to the following three simple criteria:—

1. Each tumour must be malignant.
2. Each tumour must be adequately separated from its neighbour.

3. Neither must be a metastasis.

These suggestions are now generally accepted as the *sine qua non* of plurality and are the governing clauses of the present paper.

Surprisingly, with the exception of Ward (1930), British compilers of a series have not been brought to light in the medical journals of this country. American writers, on the other hand, are legion, and as their accounts differ in so many respects a degree of confusion as to what is meant by 'multiplicity' has arisen. Some there are, e.g., Brown and Moots (1954), who confine their investigations to one organ, the stomach, and Tondreau (1954), who studied a series of patients receiving radio-therapeutic treatment for growths of colon and rectum. Others, exemplified by Lemon and Sommers (1954) and Mider, Schilling, Donovan, and Rendall (1952), have taken all organs for their province. A few have debarred plurality of growth in the same organ or in bilateral organs like breast, ovary, and testis. At the other extreme, a like number with a more catholic taste have even included the skin, a known and proven territory for multiple foci.

In parenthesis one might mention Ward (1930), who found 94 cases of multiple primary new growths at the London Radium Institute out of a total of 1773 patients receiving treatment for a skin cancer —a percentage of 5·3.

INCIDENCE

From the plethora of American authors and the paucity of British publications it might be inferred that multiplicity is a great deal more frequent in the U.S.A. than in the British Isles—an occurrence not unlike the incidence of single carcinoma of the thyroid gland in the two countries (2 per cent in Britain, 20 per cent in America).

Incidence, like definition, is difficult to determine with any degree of accuracy owing to the extreme variability of the material investigated. *Table I* shows this variability (column 4) and when the data are further considered incidence is seen in its truer light.

Warren and Gates (1932), for example, base their percentage entirely on post-mortem findings (40 out of some 1078 autopsies). Brown and Moots (1954) consider only operative findings on the stomach (4 out of 500 gastric resections). Tondreau (1954) and Ward (1930) consider patients undergoing treatment of a single organ or region—the former the colon, the latter the skin—while Cahan (1950) is concerned with multiple foci in the lungs.

Many of the other accounts are facts taken from a hotch-potch of living patients, post-mortem specimens, and clinical and pathological diagnoses. These factors conspire to rob one series of uniformity with any other, and numbers based on post-mortem findings alone take no account of the living populace possessing or being cured of a single growth, which knowledge, if obtainable, would materially alter the given percentage. The percentage figures in *Table I*, then, should be looked on as merely approximate and to some extent a matter of impression. At its best it is but a percentage of a single series of investigations and not really comparable with any other. There are too many variables for this.

In passing, Barrett, Miller, and Fessenmeyer (1949) consider an incidence of 0·3 per cent to 6·8 per cent to be the range of multiplicity, while Keyes, Jordan, and Wyatt (1951) consider that in 12 per cent of patients with carcinoma of the breast a second primary will be found in the other breast at the same or later date.

Harrington (1946), from a vast experience of 6149 unilateral mastectomies, found in 3·4 per cent second primary growths in the opposite breast and considered the prognosis so grave—particularly in simultaneous growths in the two breasts—that he tentatively moots the advisability of a prophylactic amputation of the innocent breast, although on balance he rejects this perhaps too drastic view.

Table I.—INCIDENCE OF CASES OF PRIMARY CARCINOMA MULTIPLEX IN THE LITERATURE

AUTHOR AND YEAR	CASES	PERCENTAGE	REMARKS
Warren and Gates 1932	1078	3·7	Post-mortem investigations, 40 cases discovered
Other authors' cases	1219	1·8	Review of literature
Cahan 1950	1493	1·6	Lungs, 25 cases discovered
Brown and Moots 1954	500	0·8	Stomach only. Cases submitted to gastrectomy for primary carcinoma
Hurt and Broders 1932	2121	3·3	Mayo Clinic
Pietnsky Medwedjew		0·3 4·3	Quoted by Warren and Gates 1932 as opposite extremes
Ward 1930	1773	5·2	Skin only. Quoted by Warren and Gates as the "highest [percentage] to date" from Radium Institute, London
Mider and others 1952	3996	4·5	——
Barrett and others 1949		0·3–6·8	Quoted range "Variously quoted"
Doublier and Vail 1948		0·9–7·8	Quoted range "Variously quoted"
Maddock and others 1956			Breast alone "opinion"
Harrington 1946	6149	3·4	212 non-simultaneous growths in opposite breast
Tondreau 1954	812	2·9	24 cases found in those receiving treatment
Dockerty 1943		3·4	Considered polypoid carcinoma of colon multiple in 4 per cent

The present very unsatisfactory mode of cancer registration in England—or rather the almost total lack of it—has made the inference of percentage valueless and it has not been attempted in the present series. The list comprises some 17 patients treated at Addenbrooke's Hospital, Cambridge, most of whom are still alive. To consider them as a percentage of the hospital autopsies on all cancer cases would be farcical; to consider them as a fraction of all cancer sufferers in the Cambridge district impossible. A personal impression is that Barrett and others' upper limit of something in the region of 6 per cent is not unlikely. With the increase in longevity this is in danger of being exceeded. We have only to

consider the phenomenal rise in the incidence of cancer of the lung during the past forty years, and the less spectacular but none the less real rise in sufferers from primary carcinoma of the liver, to realize that changes in incidence may take place very quickly, and to view with apprehension the increasing chance of multiple primary carcinoma with the passing years.

SUSCEPTIBILITY

Thomas, Dockerty, and Waugh (1948) conclude that multiple primary carcinoma is a reflection of an inherent constitutional susceptibility to cancer which is present in some individuals. Maddock, Lipinski, Lien, and Alt (1956) report a case of four primary malignancies and review the literature of other patients with a like number. In their own case a woman underwent in 1927 a right radical mastectomy, in 1940 the removal of the right ovary, seven years later a partial colectomy for cancer of the sigmoid, and in 1949 the removal of the remaining breast. All these operations were for primary growths of differing cytohistology. There was no metastatic involvement when the abdomen was opened for the second time in 1947, and clinically there was never any evidence of secondary carcinoma anywhere. She survived the last operation some seven years.

Ewing (1928) states: "It would appear that an individual with one malignant growth provides fertile soil for the development of a second tumour. This implies that the risk of developing cancer is not evenly spread over the population, so that some individuals are more susceptible than others, or are more exposed to influences bringing about its development." In double cancer of the same organ he considered that the first growth so influenced the condition of that organ as to render it more susceptible to a second neoplasm at a later date.

Mider and others (1952) directed their researches chiefly towards discovering if there was an extra risk of developing further growths in an already cancerous patient. Their findings are a little inconclusive, but on the whole lean to the fact that a patient with one primary new growth is more likely to develop a second than could be accounted for by chance alone.

Warren and Gates (1932) and Barrett and others (1949) also favour this view. Watson (1953), on the other hand, investigating some 1171 cases of all types of malignancy found 412 with more than a single centre of carcinoma, and came to the opposite conclusion, namely, that there was no evidence of a tendency to develop a second growth, nor was there any suggestion that one growth conferred a relative immunity against plurality.

Warren and Ehrenreich (1944) calculated that the liability to multiplicity was some eleven times more frequent than could be accorded to the operation of chance alone. This opinion would seem to carry the burden of likelihood more satisfactorily than any other.

SITE

The same confusion over the most prevalent sites for multiple growths exists, due in part to the mingling of data derived from one single organ, or to a pair of similar organs. Thus, while many authors claim the colon as *one* of the sites most commonly affected, others attribute to the testes, breasts, ovaries, and female generative organs the pride of place.

Undoubtedly *bilateral* primary carcinoma is most prevalent in those organs subject to endocrine control, and is generally of the hormone-dependent type. Certainly no surgeon can doubt the susceptibility of the colon to polyposis, and only too frequently these have been found to harbour foci of cancer often situated far apart.

Tondreau (1954), a radiologist, investigated some 812 cases of large intestine carcinoma and found 24 with an additional focus (2·9 per cent). He stressed the necessity of an extended examination of the large intestine and remarked that owing to the predominance of multiple primary carcinoma in the large intestine the findings of a single growth should encourage the clinician to further efforts (with barium enema and radiography) to hunt for a second, and the surgeon to examine with extra care the whole length of the colon. He does not, however, list the type of cells in the multiple growths. This must *ipso facto* raise a possible suspicion that some of those cases of a similar morbid histology might, in fact, be of the nature of seedlings comparable with the papillary carcinoma of the renal pelvis, which so commonly gives rise to foci distally in ureter and bladder, and in fact is here shown (*Case* 14) where kidney, ureter, and bladder were all affected subsequent to uterus and ovary ten years previously.

Where two growths in the colon, or colon and rectum, are found, unless the histological nature of the cells differs, only after the strictest scrutiny should they be classified as separate primary growths. In the present series 2 cases, one with three foci in the colon (cæcum, transverse colon, and splenic flexure) and one with a sigmoid and rectal growth, all being of the columnar adeno-carcinoma type, were both excluded for the above reason.

Brown and Moots (1954), investigating multiple carcinoma of the stomach, describe 4 cases of multiple primaries in 500 gastric resections for cancer, a percentage of 0·8 per cent. They noted the presence of polypoid carcinoma in multiple cases and suggested the adoption of total gastrectomy in all cases of polypoid carcinoma, owing to the likelihood of additional (though small) lesions being present and overlooked at the time of a partial gastrectomy.

PRESENT SERIES

The present series of 17 cases is shown in the attached *Table II*. In view of certain points of interest, brief notes of the more significant findings are appended to those cases marked with an asterisk. It was not felt either necessary or desirable to give detailed accounts of each case, which could add little to knowledge or clarity of vision. Perhaps the most surprising facts are contained in *Table II* under the heading 'comment and demeanour'. It was most striking how well and hopeful the majority of patients appeared, possessing almost a *spes carcinomica*, in deep contrast to those who had secondary extensions, however small, in gland, bone, or other organ. Indeed, this characteristic was frequently commented on, and the house-surgeon's or registrar's spontaneous "looks well", "appears remarkably

well", in the notes, devoid of any prompting, occurred too often to be mere coincidence.

Unlike the American series, males do not predominate, 11 of the cases being women, a not unlikely result when we consider that in 10 of these cases one of the organs affected was an organ particular to the female sex.

Table II.—PRESENT SERIES OF 17 CASES

CASE	SEX	AGE	DISEASES	COMMENT AND DEMEANOUR
1	M.	72	Lung, 1957; bladder, 1957	Looks well. Alive
*2	M.	64	Colon, 1940; pinna, 1953; larynx, 1955; larynx, 1957	*See* case reports. Alive
*3	F.	61	Colon, 1952; breast, 1955	*See* case reports. Alive
4	F.	61	Breast, 1943; colon, 1956	General condition good until obstruction. Dead
*5	F.	43	Right breast, 1954; left breast, 1955; ovaries, 1955	*See* case reports. Alive
*6	F.	42	Right breast, 1955; left breast, 1956	*See* case reports. Dead
7	F.	48	Squamous carcinoma of thigh, 1946; uterus, 1952; colon, 1957	Alive
*8	M.	82	Bladder, 1954; prostate, 1957	*See* case reports. Dead
9	F.	58	Uterus, 1956; left breast, 1956	Doing well; very happy. Alive
10	M.	79	Bladder, 1956; lung, 1956	"Never seen a doctor"; felt well but died suddenly
11	M.	85	Colon, 1955; prostate, 1956	"Simple prostatectomy 1952". Alive
12	F.	59	Left breast and gall-bladder, 1956	Always miserable. Dead
13	M.	72	Bronchus and prostate, 1953	Dead
*14	F.	51	Right ovary, 1941; uterus, 1944; kidney, ureter, and bladder, 1951	*See* case reports. Dead
15	F.	73	Breast, 1948; cervix, 1953	Alive
16	F.	53	Right and left breasts, 1957	Alive
17	F.	57	Colon, 1946 (acute obstruction); cæcum, 1951	Appears remarkably well. Alive

Age refers to present age, or age at death.

CASE REPORTS

Although not claiming an equality with the cases investigated by Maddock and others, the following case presents several features worthy of special mention :—

Case 2.—Male, aged 47, in 1940 underwent right hemi-colectomy for a carcinoma of the cæcum. He remained well until 1953 when he complained of indigestion, and after investigation was found to have a large pre-pyloric ulcer ("not above the suspicion of malignancy"). A partial gastrectomy revealed a simple ulcer (confirmed by pathologist) and the patient made an uninterrupted recovery. No secondary growths were seen anywhere. A few months previous to this he had developed a squamous cell carcinoma of the pinna which was apparently cured by radiotherapy. He remained well until 1955 when he developed a squamous cell carcinoma of the larynx suggestive of rapid growth and invading the right side of the larynx extensively. This was successfully treated by radiotherapy and he continued in good health for two years. In 1957 a new focus appeared on the right arytenoid, for which total laryngectomy was performed. The pathologist submitted the following note on the removed specimen: "Widespread intra-epidermal carcinoma. No definite evidence of subepidermal tissue spread, i.e., it is *not* an ordinary invasive carcinoma"; from which it might be inferred —albeit somewhat tentatively—that it was another primary, making the patient's fourth. He is at present alive and well, remarkably cheerful, and appears to be an excellent example of those cases previously referred to as fated to be attacked by carcinoma.

Case 3.—A woman lodging-house keeper, first seen in 1952, complaining of vague right upper abdominal pain radiating to the back and a long past history of jaundice. Nightly temperature was 102° F. for the previous five weeks. Barium sulphate enema and radiography suggested carcinoma of the ascending colon. No mass was felt on the right side, but in the epigastrium a vague mass was palpable. Laparotomy revealed (1) marked fat necrosis; (2) a mass in the ascending colon about the size of a tangerine; (3) a very large mass involving the transverse colon, transverse mesocolon, and stomach. The liver and gall-bladder appeared normal. The condition was considered to be hopeless and inoperable, and the removal of large mesocolic glands from transverse and ascending colic mesocolons and a thickened area of peritoneum was the extent of the operation (biopsy). The glands were returned as: "No evidence of secondary carcinoma. Glands appear to be inflammatory only." The peritoneal nodule was "fat necrosis".

From that moment the patient appeared to make a remarkable recovery and never at any time was less than "most hopeful, most helpful and most co-operative". She said she felt well and was much improved by her 'operation'. One year later all abdominal symptoms had cleared up, but the central mass had increased in size and apparently had travelled leftwards. Clinical examination and radiography suggested a pseudo-pancreatic cyst. She was advised operation especially in view of the repeated X-ray examination of the colon, which again showed a filling defect in the ascending colon. The cyst was removed and right hemi-colectomy performed with the removal of a well-differentiated tubular carcinoma in the ascending colon. The very large mass which appeared to envelop the stomach and transverse colon at the previous operation had disappeared. Glands showed no sign of secondary involvement (even after the lapse of one year). The patient made an uninterrupted recovery, remained very cheerful, and said she felt better than ever. Sixteen months later she developed a lump in the left breast, clinically and pathologically diagnosed as carcinoma, and radiotherapy was prescribed with apparent betterment, but a further eighteen months showed a recurrence with *peau d'orange* and secondary axillary glands. A simple mastectomy was performed.

Case 5.—Female. An interesting point arises in this case. Right and left mastectomies were performed with an interval of about a year between the two operations. Two months after the second operation double oöphorectomy was carried out with the object of lessening the œstrogen load, and in spite of the fact that both ovaries showed heavy deposits of spheroidal-cell cancer similar to the primary growth, and apparently due to transcœlomic implantation, marked improvement followed, and bony metastases previously noted had greatly diminished in size and in some cases showed well-marked calcification.

Here the attempt to lessen the hormone stimulant was apparently successful, for the time being at all events, although there was little ovarian tissue visible, each ovary being almost totally replaced by carcinoma cells. The patient is alive and well at the moment of writing. It is at least curious and worthy of note that organs with so little (if any) of their original secreting tissue can so influence secondary bony metastases by the withdrawal of secretions.

Case 6.—Female. This is only of interest as being the antithesis of *Case* 5. Bilateral oöphorectomy had no effect in improving the patient's condition. After two mastectomies, and later double oöphorectomy, she died 19 days later. It is worthy of note that she had glandular metastases at the time of the first primary.

Case 8.—Male. This case is a little difficult of interpretation as the patient passed through several surgeons' hands. He was diagnosed as suffering from a single large benign papilloma of the bladder in 1954. He refused all treatment, but owing to a recurrence of hæmaturia was re-cystoscoped by another surgeon later in the year. His diagnosis was of an "innocent papilloma", and a radiograph showed calcification of the prostate.

Three years later (1957), when 82 years of age, further hæmaturia with difficulty in passing water caused the patient to submit to operation. "A transitional cell tumour of the bladder, probably malignant, and a fairly well differentiated cubical cell acinar carcinoma of the prostate" were removed. He died 12 days later of an embolism. This case is noteworthy by reason of the suggestion of metaplasia in the bladder growth, and the later development of carcinoma of the prostate, which had previously been small and with numerous calcareous nodules.

Urologists will generally agree that a "calcareous prostate" rarely becomes malignant.

Case 14.—Female. At the age of 38, in 1943, a carcinomatous ovary was removed. One year later hysterectomy for menorrhagia revealed an adenocarcinoma of the body of the uterus. Seven years later, in 1951, a papillary carcinoma of the kidney with seedlings in the ureter and bladder was removed at a single operation. Pathology report: "*Kidney*. Papillary carcinoma of transitional epithelium arising from renal pelvis. Growth is only moderately well differentiated in comparison with ureteral and bladder growths. *Ureter*: Papillary carcinoma of transitional epithelium more differentiated than kidney growth. *Bladder*: Papillary carcinoma of transitional epithelium well differentiated." "Comment. These sections show multiple transitional cell papillary carcinomata throughout the urinary tract. They do not suggest secondary new growth from a previous papillary carcinoma of the ovary 8 years previously." The patient died five years later with large secondary masses in the pelvis, aged 51.

This case is worthy of comment as the patient was one of the younger set, carcinoma developing at the age of 38. She suffered three operations for three different types of primary carcinoma at the ages of 38, 39, and 46, and lived a further five years, only to die of extensive secondary deposits involving the pelvic walls, contents, and sacral plexus. Until secondary involvement became apparent, rather late for one so young, she was happy and contented and entirely free from pain and discomfort. Another point of interest is the fact that the seedlings in the ureter were more differentiated than the primary renal tumour and those in the bladder still more so, a suggestion that the lower urinary tract is better fitted for dealing with carcinoma than the upper (compare the very lethal papillary growth of the kidney with the much less deadly bladder growth of similar nature).

COMMENT AND CONCLUSIONS

Apart from the side-effects of obstruction to the œsophagus, stomach, or bowel, *primary* cancer alone never kills, and it is only when secondary extension makes its appearance that the lethal sequence is initiated. The removal of primary growths by surgery or radiotherapy is for the most part easy and relatively free from dangers, and a false optimism is thereby engendered.

With the appearance of secondary growths, even after the primary has been removed, the whole picture changes. A morbid outlook, a toxæmic-like state, and cachexia become apparent, and all too often an irremovable mass in glands or essential organ is the rule. So marked is this difference between primary and secondary cancer that the two phases might almost be separate diseases.

The behaviour of multiple primary foci and their effects on the patient are almost identical with those of a single primary focus, and a comparatively hopeful and happy patient is in marked contrast to the unfortunate with a secondary extension. There would appear to be a fruitful field here for research into the biochemistry of the two phases.

Old age is a necessary requisite of multiple cancer and it is understandable that a person not laid low by a 'first attack' has a more than average chance of being attacked a second or third time. Six of the 16 patients were over 70 years old; 3 over 79. *Per contra* the youngest was 42 and 3 were under 50. It is interesting to note in this connexion that Watson (1953) found the largest number in the 75-plus age-group, and Cleave (1954), in a thoughtful letter, makes the *reductio ad absurdum* that if all other diseases and accidents were abolished we should all live until cancer terminated our lives—100 per cent mortality.

Although the present series contains no case of polyposis of the colon, multiple polypoid cancer of this organ is so common as to be adjudged the prime *single* region in multiplicity by many, if not most, American authors. As has already been mentioned, some of these cases are not above the suspicion of being 'seedlings', and though these off-shoots may not be strictly metastases they seem to fall midway between primary and secondary growths.

It may be *à propos* here to refer to the work of Dormandy (1957) on polyposis of the small intestine in the disease first described by Peutz in 1921. In this syndrome numerous polyps occur in the small intestine associated with circumoral and circumanal pigmentation encroaching on the mucous membranes. These adenomatous polyps never become malignant, and this fact, together with the apparent immunity of the small intestine to true cancer, although abutting on the pylorus at one end and the cæcum at the other, raises an interesting point as to whether the mucosa of the small intestine secretes some anticarcinogen which is responsible for this cancer-resistant part of the alimentary tract. Surely a happy hunting ground for further research into the production of anticarcinogens?

When the writing of this paper was first mooted it was thought that the condition would prove to be a comparative rarity, as British writers on the subject were so few. A perusal of the American literature soon dissipated this view, but although the condition may be almost common in the U.S.A. (and to a lesser extent on the continent of Europe) it is at least infrequent in Great Britain. With better registration and more efficient 'follow-up' methods, it is hoped that multiplicity will receive its rightful importance, both for the sake of accuracy, and also as a stimulus to surgeons to look beyond the finding of a single primary neoplasm for the possibility of others.

The fact seems inescapable that cancer is no longer to be considered a purely local condition, but is rather of the nature of a 'general' disease becoming manifest in more than a single region at the same or later date. Much time, trouble, and expense have been lavished on the understanding of this mortal complaint, yet so much remains to be done.

Accurate registration (which could so easily be carried out without the patient being aware of it), research into the cause of death in cancer, and the possibility of anticarcinogens being housed in certain parts of the body, would appear worthy of consideration by those interested in the control of cancer.

SUMMARY

Seventeen cases of multiple primary carcinoma are described and the literature of the past twenty-five years reviewed.

The multicentric origin of cancer is stressed and a comparison between multiple, primary, and secondary cancer is drawn.

Suggestions for possible lines of research and better cancer registration are made.

Attention is drawn to the comparative absence of British publication of cases of multiple primary disease.

My thanks are due to my surgical colleagues on the staff of Addenbrooke's Hospital, Cambridge, for permission to quote their cases in the above series, and to Miss Hardwick, librarian to the Radiotherapy Department, for her great help with the bibliography.

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LANE'S ILEAL KINK

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INTRODUCTION

LANE'S ileal kink is a lesion which no longer receives the attention of clinicians. Reference to the *Quarterly Cumulative Index Medicus* from 1929 to 1954 showed that no papers dealing with this lesion had been published during those years.

Could Lane have described a non-existent lesion? This question presented itself anew when a patient with the syndrome of a lower ileal obstruction was found at operation to have a lesion identical with the lesion figured in standard surgical works as the ileal kink of Lane (Walton, 1923). This case stimulated reference to earlier papers dealing with Lane's ileal kink.

LANE'S ILEAL KINK—DOES IT EXIST?

Lane (1908, 1910, 1911) postulated that a cæcum heavy with fluid and prolapsing into the pelvis would drag on the mesentery of the terminal ileum, and determine the formation of a band of fibrosis in the inferior leaf of the mesentery in the line of strain. This band of fibrosis would extend downwards till it reached the ileum at a point about 2 in. from the ileocæcal valve, and it would then draw the ileum upwards at this

place and cause a kink in the bowel. This kink would obstruct the lumen of the bowel and determine the stasis of fluid in the bowel proximal to the kink. Lane's diagrams illustrated his concept with clarity. Lane released the kink at operations by dividing the band of fibrosis and his work stimulated others to undertake these operations. Mayo (1911), Martin (1911), Connell (1911), and Bainbridge (1913) published experiences giving descriptions of the lesion as it was observed at their operations. These descriptions were significantly different from the lesion described by Lane, although there is no hint in these papers that the writers were aware that they were describing a lesion different from that of Lane. The descriptions of these different writers are, however, so similar that they afford evidence for the existence of a lesion of the terminal ileum with well defined characteristics.

These characteristics are not those described by Lane. Could these surgeons have been dealing with a different lesion? Jordan (1911) described the lesion exposed by Lane at two of his operations. Jordan's description accords with the description of the lesion as it was observed by Mayo and the other surgeons. Like them, Jordan was not aware that his description of the lesion exposed by Lane was at variance with Lane's concept of the lesion. That Lane himself was unaware of the discrepancy is evident from his approval of Mayo's paper and his comment, "Mr. C. H. Mayo has made a beautiful drawing of it" (the ileal kink).

The evidence suggests that the lesion found at operations was not that conceived by Lane, and that Lane himself had been exposing and dealing with this lesion without realizing that it was different from the lesion he had postulated. How is it that no writer has noted the discrepancy between the features of the lesion exposed at operations and the features of the lesion postulated by Lane? How could they have failed to remark that the lesion which was exposed at operations did not and could not kink the ileum? The absence of comment is difficult to account for.

THE STRUCTURAL DETAILS OF THE ILEAL LESION

The similarity of the descriptions of the lesions observed at operations, and of the drawings made of the lesion from the appearances presented at operations, establish that this is a lesion with well defined structural details. The essential feature of the lesion is a fibrotic thickening of the peritoneal attachment of the terminal ileum to the posterior abdominal wall. This peritoneal thickening extends from the antemesenteric border of the bowel about 2 in. from the ileocæcal valve to the posterior abdominal wall just lateral to the brim of the pelvis. The peritoneal thickening is about $\frac{1}{2}$ in. wide, and it is at the place where the mobile segment of the ileum passes to the short terminal segment of ileum which is without a mesentery. The peritoneal thickening tethers the ileum so firmly that it cannot be lifted off the posterior abdominal wall. The ileum can be liberated by division of the thickened band of peritoneum, and when this is done the ileum can be lifted off the posterior abdominal wall. This manœuvre will demonstrate that there is no fibrosis in the inferior leaf of the mesentery as postulated by Lane. The peritoneal thickening could not therefore have formed from a reaction to dragging strains on the mesentery.

The thickening could have resulted from the drag of the mobile segment of the ileum on the fixed segment of the ileum causing a stress in the peritoneal attachment of the fixed segment of ileum to the posterior abdominal wall. To that extent this thickening of peritoneum would be in conformity with Lane's concept of fibrosis as "crystallizations in lines of force".

WHAT DIFFERENTIATES THE ILEAL KINK OF LANE FROM OTHER INTRAPERITONEAL BANDS AND ADHESIONS IN THE ILEOCÆCAL REGION?

Intraperitoneal bands and adhesions causing acute and subacute intestinal obstruction are commonest as a sequel (which may be early or late) of intra-abdominal surgical operations. They also occur as a sequel of previous acute intraperitoneal inflammations or of tuberculous lesions. These bands and adhesions are also clearly sequels of inflammation. The band described by Lane is not the sequel of inflammation, and it deserves special recognition on that account. Bands and adhesions may be found in cases in which no previous surgical operation has been performed, in which there is no previous history of an intra-abdominal inflammatory focus, and at operation there has been no lesion which could have set up an inflammatory reaction. Nevertheless, the disposition of the bands and adhesions in such cases suggests that they have been the sequel of past inflammation. The disposition of the bands refutes the idea that such bands originate in lines of peritoneal stress. It must be conceded that past inflammation could have occurred which had either been forgotten or which had given no symptoms which were observed by the patient. Forty (1946) described 14 cases of intraperitoneal bands and adhesions causing intestinal obstruction, in all of which there was no previous history of intra-abdominal trouble, and no lesion within the abdominal cavity at the time of operations which could have set up a past inflammation. Lange (1948) described a case of acute intestinal obstruction from a band which extended from the transverse mesocolon across the ileum obstructing it and ensnaring a Meckel's diverticulum under it. The disposition of the band in this case refutes its origin as a congenital band connected with a Meckel's diverticulum.

Lane's ileal kink stands apart from all other bands and adhesions. It is a reaction to stress, in a peritoneal attachment. It has a definite position and a definite function.

DOES LANE'S ILEAL KINK CAUSE SYMPTOMS?

Lane believed that many symptoms of general ill health and even those of tuberculosis and rheumatoid arthritis were from absorption of toxins from fluid dammed back in the bowel proximal to the kink in the ileum. He claimed that release of the kink in the ileum cured patients of such symptoms of general ill health and even of rheumatoid arthritis and tuberculosis (1912, 1913).

Lane and the other surgeons who undertook operations for the release of an ileal kink did so because of symptoms of general ill health which they

believed to have resulted from stasis in the bowel above the ileal kink. None of the patients had symptoms of intestinal obstruction. These surgeons did not address their minds to the question, " Can there be stasis in the ileum without symptoms of intestinal obstruction ? "

A kink in the ileum would produce much the same obstruction as a stenosis of the bowel, and a progressive increase in the kink would give the same sequence of events as an increasing stenosis of the bowel. Experiences with cicatricial stenoses of the ileum give a clear picture of the sequence of events in such cases (Paul, 1945). Stenoses with a diameter exceeding that of the cross-section of a fountain pen cause no symptoms and there is no stasis above such stenoses. Stenoses with a diameter less than this manifest themselves in the first instance by repeated bouts of circum-umbilical colicky abdominal pains, but there is still no stasis above the stenosis at this stage. With further narrowing of the stenoses, the peristaltic efforts of the bowel increase and there are now visible and palpable coils of bowel during the bouts of colicky abdominal pain. These increased peristaltic efforts are still adequate to propel the fluid content of the bowel through the stenosis, above which there is still no stasis of fluid, although the bowel above it is distended and filled with fluid. With further narrowing of the stenosis there is stasis, but at this stage events move rapidly to a crisis with gross distension of the bowel with fluid and gas, vomiting, and absolute constipation.

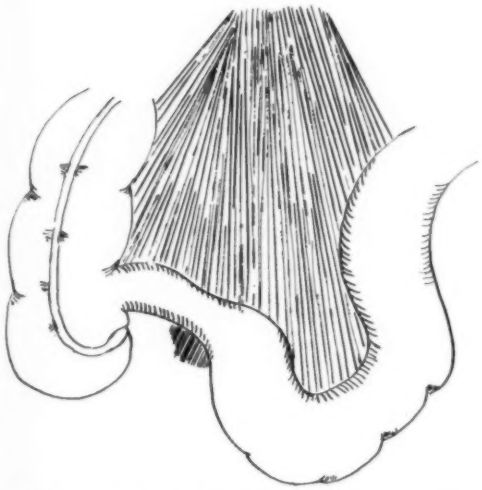

FIG. 134.—*Case* 1. View at operation showing ileum obstructed by Lane's band.

No such sequence of events was observed in the patients operated on by Lane and other surgeons for the relief of symptoms of general ill health. It is evident that there could have been no stasis in the ileum in their cases. Lane's work did establish the presence of a lesion in the terminal ileum. Although the notion that it causes symptoms of general ill health has been discarded by clinicians, there remains the question, Could the lesion obstruct the ileum even though it did not kink the ileum ? Could it not tether the ileum so firmly to the posterior abdominal wall as to obstruct the ileum at this place. No case has been recorded of such an eventuality. The long series of cases of intestinal obstruction which have been reviewed make no reference to obstructions from Lane's ileal kink (Vick, 1932; Souttar, 1925). The only reference to the possibility of a Lane's ileal kink causing an acute abdominal distension that we could find was in the chapter on acute intestinal obstruction by Allen and Welch (1947) in *Surgical Treatment of the Abdomen* (ed. Bancroft and Wade) where there is a figure of Lane's ileal kink.

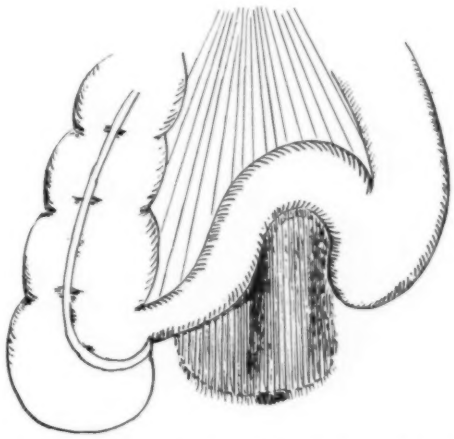

FIG. 135.—*Case* 1. Release of kink caused by Lane's band by dividing peritoneum below the ileum and mobilizing ileum off posterior abdominal wall.

The case of lower ileal obstruction coming under our observation and reported in this paper appears to be the first case recorded of intestinal obstruction from a Lane's ileal kink. In a second case also reported in this paper a patient was admitted for acute intestinal obstruction. At operation the dilated bowel terminated at the ileocæcal valve where the ileum was firmly tethered by a Lane's ileal band. Mobilization of the band released the obstruction and the patient left hospital cured of his symptoms. He returned in a few weeks with recurrence of the symptoms of acute intestinal obstruction, and an operation at this stage showed that he had an annular carcinomatous stricture of the splenic flexure of the colon. Looking back on events of this case in the light of the findings at the two operations it is evident that an increasing distension of the bowel proximal to the carcinomatous stricture had determined a complete block at the site of the Lane's ileal kink which was released at the first operation. Some weeks later further narrowing of the carcinomatous stricture determined a complete obstruction at the site of the growth.

These two cases establish that a Lane's ileal band had determined an organic obstruction of the bowel, which needed a surgical operation for its relief. Lane's ileal kink acquires a new interest from the experiences of these two cases.

CASE REPORTS

Case 1.—S. A. C., a male Sinhalese aged 38, was admitted to the General Hospital, Colombo, on May 28, 1957, on account of recurrent bouts of severe colicky abdominal pain during the past year. The pain would last for several minutes, and might recur on two or three occasions during a day. He would then be free of pain for about six days. His bowels had been opened daily and he had had an occasional loose stool.

When the patient presented himself at the clinic for examination no abnormality was detected and he was told

FIG. 136.—*Case* 2. Radiograph of patient in the erect posture before the first operation, showing fluid and gas in grossly distended coils of small bowel with numerous fluid levels.

that he would be put down for admission so that he might be observed during a bout of pain. The patient came back in two hours' time with an attack of pain. Inspection of the abdomen at this time showed a visible and palpable coil of bowel lying transversely below the umbilicus. Here was clear evidence of an organic obstruction of the terminal ileum and the patient was admitted to hospital.

ON EXAMINATION.—He was a spare, well-knit man. His abdomen was flat and there were no intra-abdominal lumps. During the week in hospital before the operation he had bouts of pain on three days. A radiograph after a barium meal revealed no abnormality.

AT OPERATION.—Under a general anæsthetic on June 6, 1957, a McBurney incision was made. The peritoneal cavity was clean. The terminal ileum could not be delivered through the wound on account of its being anchored to the posterior abdominal wall. The rest of the small intestine could be delivered easily through the McBurney incision, as could also the cæcum and ascending colon, which were completely invested with peritoneum on their posterior walls. The appendix was retrocæcal and covered by the peritoneal coat of the posterior cæcal wall.

Inspection of the terminal ileum showed a well marked Lane's ileal kink passing from the antimesenteric border of the ileum at a point 2 in. from the ileocæcal valve (*Fig.* 134). This band was short and fibrotic, and reached to the fascia overlying the ileopsoas muscle lateral to the brim of the pelvis. The band was divided exposing the ileopsoas muscle, and the terminal ileum was mobilized by blunt dissection detaching it from off the posterior abdominal wall (*Fig.* 135). The appendix was excised. The patient made an uneventful recovery from the operation and left hospital on June 15. There has been no recurrence of the pains and the patient is well pleased with the result (Aug. 13).

Case 2.—L. J. P., Sinhalese, aged 45, was admitted to the General Hospital, Colombo, on July 19, 1956, for bouts of circum-umbilical abdominal pain of fifteen days' duration. The bouts used to last for about five minutes

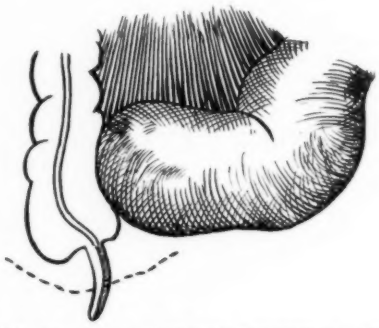

FIG. 137.—*Case* 2. View at the first operation. Diagram shows the distended ileum with an abrupt termination of the distension at the ileocæcal valve. The mesentery of the ileum was unattached but at the ileocæcal valve the bowel was firmly glued to the posterior abdominal wall. The appendix and its mesentery were lateral to the ileocæcal valve. The dotted line represents the position of the incision in the parietal peritoneum which was made to mobilize the cæcum and the ileum.

and would cease with borborygmi. The pain used to come on every ten minutes and was unbearable and constrictive. At first the patient had taken ayurvedic treatment for eight days without relief, and he had then entered a local government hospital for four days more. While there he was given an enema, but the fluid was returned without flatus or fæces. The patient had not had a stool during the whole of this period. He then entered a private nursing home in Colombo, where more enemas were given with the same result. At this stage the abdomen became distended, and although he was not now taking any solids, he was vomiting five or ten minutes after taking fluids. After three days at this hospital he entered the General Hospital.

PAST HISTORY.—He had had a similar attack of colicky abdominal pain three months previously, and had been in the General Hospital for this. The pain had disappeared after eighteen hours and had not recurred till the present illness.

ON EXAMINATION.—Pulse 76, temperature 100. The patient was emaciated, his skin was dry and inelastic, and there was moderate abdominal distension. Every few minutes there was visible a distinct 'ladder pattern' and the patient experienced colicky abdominal pain at these times. A diagnosis of ileal obstruction was made. A radiograph of the abdomen with the patient in the erect posture showed gross distension of the small bowel with fluid and gas with numerous fluid levels (*Fig.* 136).

AT OPERATION.—July 20, 1956, under general anæsthesia. The abdomen was opened through a right paramedian incision. There was an excess of serous fluid in the peritoneal cavity. The small bowel was dilated to the diameter of a wrist and was congested. The dilatation decreased from the ileum upwards. There was an abrupt termination of dilated bowel at the ileocæcal valve and the cæcum was collapsed and empty, as was the rest of the large bowel (*Fig.* 137). The ileum was firmly tethered to

the posterior abdominal wall by a band of fibrosis passing from the antemesenteric border of the ileum at the ileocæcal valve to the posterior abdominal wall. The fibrosis did not extend over the bowel. The terminal ileum was liberated by incising the peritoneum below the cæcum and the terminal ileum and lifting the bowel off the posterior abdominal wall (*Fig.* 138). This released the obstruction in the ileum. The peritoneal cavity was free of any other bands or adhesions. The dilatation of the small bowel terminated abruptly at the ileocæcal valve and the dilated bowel was red from congestion of its vessels. The abdominal wound was closed. The patient made an uninterrupted recovery and left hospital on Aug. 8, 1956. A radiograph taken after a barium meal before discharge

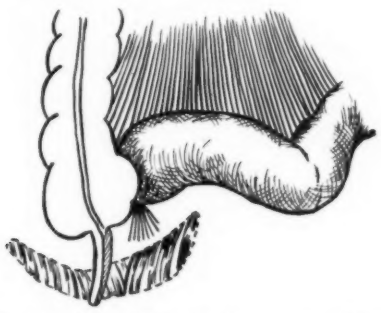

FIG. 138.—*Case* 2. View at the first operation. Diagram shows the cæcum and the ileum after they have been liberated from the posterior abdominal wall by blunt separation through the incision made in the parietal peritoneum of the posterior abdominal wall. The edges of the incision have been widened to create a gap and the muscles of the posterior abdominal wall are seen in the floor of the gap. The diagram shows the band of fibrosis from the antemesenteric border of the ileocæcal valve, which had anchored the bowel. Although the band has not been divided the blunt separation of bowel and peritoneum off the posterior abdominal wall has released the obstruction and the bowel has already been deflated by passage of its contents through the ileocæcal valve.

from the hospital confirmed that there was now no obstruction of the small or large intestine.

FIRST READMISSION.—The patient was readmitted to the hospital on Aug. 10, 1956, under the care of Dr. C. P. De Fonseka, complaining that since leaving hospital he had been vomiting "continuously" and that he had not passed any flatus. He showed a well marked ladder pattern through his thin abdominal wall but there was no abdominal distension. The abdomen was re-opened by Dr. De Fonseka on Aug. 11, 1956, through a McBurney incision. There was an excess of serous fluid in the peritoneal cavity. On exploring the abdomen with the hand inserted through this incision, coils of dilated and contracted small bowel were felt and bowel was felt adherent to the back of the previous abdominal incision. Through a left paramedian incision the adherent bowel was freed. It had formed a double-barrelled loop, one limb of which was adherent to the abdominal wall. The dilated coils of small bowel were proximal to this loop, and the contracted coils of the small bowel were distal to it. There were four other recently formed bands between coils of bowel which had, however, caused no obstruction. All bands were divided. The incision in the peritoneum which had been made below the cæcum and the ileum at the first operation was noted to be still a wide depressed area. Inspection showed that the area was being peritonized. The McBurney and the left paramedian incisions were closed.

The patient made a good recovery from this second operation.

SECOND READMISSION.—The patient was readmitted to hospital again on Aug. 26, 1956, under the care of Dr. C. P. De Fonseka, complaining of abdominal pain of eight days' duration. His bowels had not been opened for ten days. He was vomiting and bringing up 'coffee-ground' material. The patient was observed to have bouts of colicky abdominal pain and a ladder pattern was visible through the abdominal wall at these times. At first the patient refused to have any further operation, but he agreed when there was no improvement in his condition. A laparotomy was done on Aug. 28, 1956. The small and large bowel were grossly dilated up to an annular stricture of the splenic flexure of the colon by a carcinoma. The bowel was contracted and empty below this. A cæcostomy was done. On Sept. 20 the left colon was resected and the transverse colon was anastomosed to the pelvic colon. The growth removed was a well-differentiated adenocarcinoma. The cæcostomy was closed on Oct. 12, 1956, and the patient left hospital on Oct. 26, 1956.

CONCLUSIONS

Lane's ileal kink does not exist. Re-examination of the literature revealed that the lesion, exposed and divided by Lane and the other surgeons who undertook operations for the release of the kink, was a band of fibrosis in the peritoneal attachment of the terminal ileum fixing it to the posterior abdominal wall. This lesion did not and could not kink the ileum.

Should this lesion continue to be known as Lane's ileal kink? That there is a difference between the lesion which was exposed and divided at operations and the lesion which was conceived by Lane has not hitherto been appreciated, and the name 'Lane's ileal kink' has been applied to drawings made of the lesion exposed at operations, without realization that it does not depict the lesion conceived by Lane. These drawings do, however, refer to a lesion which actually exists and which was accurately described by observers of Lane's time. The retention of the name 'Lane's ileal kink' for this lesion would be a fitting tribute to the man who revealed this lesion at his operations for a kink which did not exist. Moreover, the name has already been incorporated into the terminology of surgery. This paper clarifies the anatomical features of this lesion, and reports 2 cases in which the lesion had caused intestinal obstruction. These are the first cases to be reported with this complication, and this should determine an interest in Lane's ileal kink from a fresh clinical angle.

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THE EFFECTS OF SECTION OF THE PITUITARY STALK IN MALIGNANT DISEASE*

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SINCE it has been realized that the hypophysis may influence the progress of some types of cancer, various methods have been employed to render the gland functionless. It has been removed by operation, transcranially and transnasally, and attempts have been made to destroy it by different means of irradiation, including the injection or implantation of radio-active substances into the sella. Recently it has been suggested by Russell (1956) that if the pituitary stalk were divided at its junction with the gland and its distal end coagulated, the necrosis of the anterior lobe might be so great that the operation might be as effective clinically as total hypophysectomy. This theory was based upon autopsy findings and upon the anatomy of the blood-supply of the gland.

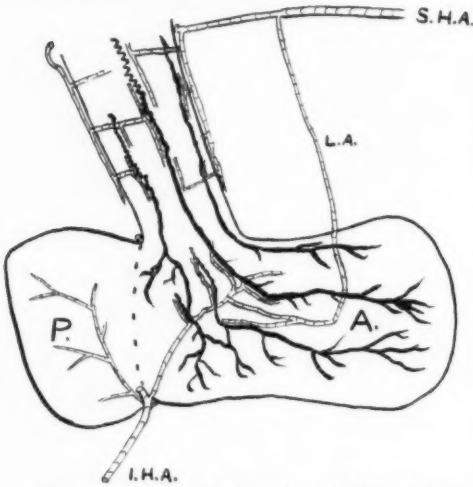

FIG. 139.—Diagram of the portal vessels of the pituitary stalk and anterior lobe. (*Adapted from Xuereb and others*, 1954.) P_1 Posterior lobe. A_1 Anterior lobe. S.H.A., Superior hypophysial artery. L.A., Loral artery. I.H.A., Inferior hypophysial artery. The portal vessels are represented by the thick dark branching lines.

The anatomy of the blood-supply of the hypophysis has been studied particularly by McConnell (1953) and Xuereb, Prichard, and Daniel (1954) (*Fig.* 139). The glandular part of the anterior lobe, as opposed to the capsule, receives its blood entirely or almost entirely through the portal vessels which lie in the stalk and substance of the gland. Blood reaches these portal vessels through four main arteries, the two superior and the two inferior hypophysial arteries. The superior hypophysial artery arises from the internal carotid artery close to the origin of the ophthalmic artery and then runs backwards to join the stalk at its upper end, but before doing so a small branch, the Loral artery or artery of the trabecula, is given off on each side; this runs downwards a little apart from the stalk, enters the substance of the anterior lobe, and there drains into the portal vessels in the intraglandular portion of the stalk. After the Loral arteries have arisen, the two superior hypophysial arteries together form a vascular network over the surface of the stalk, and from this network small branches are given off to supply the portal vessels within the substance of the stalk. The inferior hypophysial artery arises from the superior aspect of the internal carotid at its first bend within the cavernous sinus. It then runs medially and enters the sella where it divides into medial and lateral branches which, by anastomosing with their fellows in the interlobular sulcus, form an arterial ring about the pituitary body. From this ring branches arise to supply the posterior lobe and portal vessels lying in the intraglandular part of the stalk and anterior lobe.

If, therefore, the pituitary stalk and its accompanying vessels derived from the superior hypophysial arteries were divided, the blood-supply of the anterior lobe of the gland would be reduced considerably. If, in addition, the portal vessels in the intraglandular part of the stalk were coagulated, further interference of the blood-supply of the anterior lobe might occur, so that theoretically gross ischæmic necrosis of the anterior lobe might take place.

In the following three cases the pituitary stalk has been divided and coagulated at its junction with the gland in this way. Subsequent histological studies of the gland have shown that viability of a considerable part of the anterior lobe was maintained, and it is evident that the inferior hypophysial arteries supply blood to a significant part of the lobe through the portal vessels lying deeply within the substance of the gland.

CASE REPORTS

Case 1.—Male, aged 58. This patient had carcinoma of the prostate, proved by biopsy, with multiple metastases in bone. For nine months he had suffered from increasing pain in the back radiating down both lower limbs, which had not responded to prolonged treatment with stilbœstrol. Owing to technical difficulties, he was operated upon in two stages. At the first operation a right frontal craniotomy was performed, the pituitary stalk with its accompanying blood-vessels was divided as it entered the gland and the distal end was diathermied heavily. Ten days later the wound was re-opened and the pituitary body was removed in two large pieces. Adrenocorticotrophic hormone (ACTH) was administered from the time of the first operation, and the patient's general condition and state of consciousness remained satisfactory throughout, there being no significant alteration of blood-pressure, which was 135/85. After the first operation, he developed diabetes insipidus, and the pain in his legs began to subside so that, even before the second operation was performed, he was able to straighten his legs for the first

* Based upon a paper read by Campbell Connolly at a meeting of the Society of British Neurological Surgeons held at Bristol in November, 1956.

time for many weeks. Histological examination of the gland showed that the posterior lobe was normal, approximately one-quarter of the anterior lobe remained healthy, but three-quarters had become necrotic (*Figs.* 140, 141).

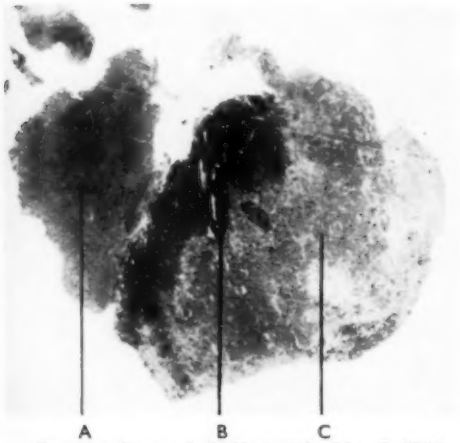

FIG. 140.—*Case* 1. A, Viable posterior lobe. B, Viable anterior lobe. C, Necrotic anterior lobe. H. and E. (× 13.)

Case 2.—Female, aged 40. This patient had carcinoma of the breast with multiple bony metastases. One year previously radical mastectomy had been performed and was followed by deep X-ray therapy. Three months later she developed pain in the back and girdle pain which steadily increased in spite of further deep X-ray and testosterone by mouth, so that for five months she had been confined to bed. Her general condition was poor,

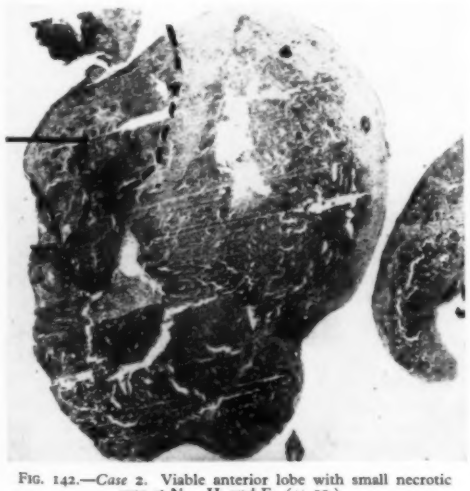

FIG. 142.—*Case* 2. Viable anterior lobe with small necrotic area at N. H. and E. (× 12.)

but there was no local recurrence of the growth and the liver was not enlarged. Radiography revealed metastases throughout the skull, spine, ribs, and pelvis. Through a right frontal craniotomy the pituitary stalk was divided as it passed through the diaphragma sellæ and the distal end was heavily diathermied. The patient's condition under anæsthesia had given rise to some anxiety when the dura mater was incised and the operation was therefore discontinued at this stage. Eighteen days later, the wound was re-opened and the hypophysis was removed. After the first operation, she developed diabetes insipidus,

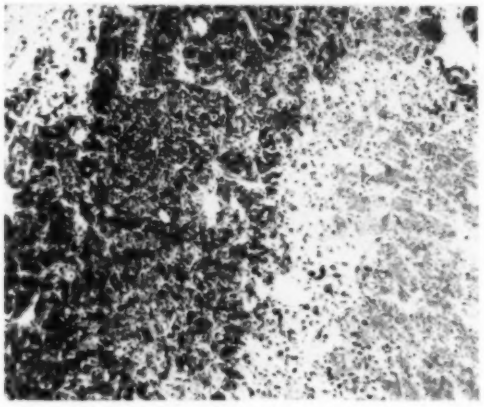

FIG. 141.—*Case* 1. Junctional zone of viable and necrotic anterior lobe. H. and E. (× 60.)

the pain was greatly relieved, and on her own initiative she began to get up from her bed. Cortisone was administered from the time of the first operation and her condition remained satisfactory, the blood-pressure being steady throughout at approximately 150/80–140/70. Histological examination of the gland showed a small area of necrosis in the anterior lobe, but most of it (approximately 80 per cent) remained viable, although in some places the surviving cells stained rather palely (*Fig.* 142).

Case 3.—Female, aged 56. This patient also had carcinoma of the breast with multiple metastases. Seven months previously she had developed pain in the right shoulder and was discovered to have an inoperable carcinoma of the breast. She was therefore given deep X-ray therapy. One month later, she developed pain in the lumbar region and radiography revealed metastases in the vertebræ and pelvis, for which she received further deep X-ray therapy. The pain persisted and she was able to obtain relief only by lying down. Five weeks before admission, she became aware of paræsthesia over the left occipito-parietal region which was followed by increasing slurring of speech. On examination, her general condition was good. There was well-marked dysarthria, partial dysfunction of the ninth, tenth, eleventh, and twelfth cranial nerves on the left side and some hemiatrophy of the tongue. There was also slight sensory disturbance over the distribution of C.2 on the left side. Radiography showed evidence of a secondary deposit in the margin of the foramen magnum on the left side, accounting for the lower cranial nerve lesions, and also multiple metastases in the lumbar vertebræ. A right frontal craniotomy was performed and the region of the sella exposed. The pituitary stalk was clearly seen and was diathermied and divided at the diaphragma sellæ. The diaphragma was then incised, and as much as possible of the pituitary body was removed, many small pieces of the gland being obtained. Zenker's fluid was introduced into the cavity before the wound was closed. With further experience with the operation, it was realized that the gland had been removed incompletely and that the lateral extensions of the gland had been obscured by the inverted edges of the diaphragma sellæ. However, after operation the patient improved remarkably; her pain decreased and practically disappeared in about two weeks, the paræsthesia and numbness over the back of the head,

together with the dysarthria, also rapidly cleared up, and within three weeks the tongue had returned practically to normal. She had persistent diabetes insipidus, but there was never any significant alteration of blood-pressure, which remained approximately 120/80. She was treated at first with ACTH and later with cortisone. Having remained well for about two months, she had an increasing

FIG. 143.—*Case* 3. Viable anterior lobe with area of scarring at S. H. and E. (× 13.)

recurrence of pain in the back and later developed ascites with enlargement of the liver. The lower cranial nerve pareses never recurred. She died five months after operation. Post-mortem examination, performed at another hospital, revealed multiple visceral and bony metastases. The pituitary stalk was reported to have regenerated. The pituitary gland was normal in size and, on histological examination, was found to consist largely of anterior lobe without visible necrosis, but with a small area of scar tissue (*Figs.* 143, 144). The pituitary stalk unfortunately was not preserved for histological section. No definitely recognizable posterior lobe was found.

DISCUSSION

The site and degree of necrosis of the anterior lobe in *Cases* 1 and 2 correspond with the findings in rats following section of the stalk as described by Daniel and Prichard (1956), but the degree of infarction of the anterior lobe in all three cases was less than in those recorded by Russell (1956). The reason may be that our cases recovered rapidly from the effects of operation and suffered no prolonged alteration of blood-pressure; whereas, in Russell's series, all the patients were very ill between operation and death, marked lowering of blood-pressure being recorded in three of the four cases.

It is notable that all these three cases showed considerable clinical improvement within a few days of the pituitary stalk being divided, but this improvement was maintained for only two months in the patient (*Case* 3) in whom the gland was not removed subsequently. This improvement may have been due partly to necrosis in the anterior lobe, partly to dysfunction of the surviving part of the lobe owing to ischæmia, and possibly to interruption of hypothalamic control of the anterior lobe. However, with survival of a significant part of the anterior lobe, improvement is likely to be temporary only, as in *Case* 3, for it has been shown experimentally in dogs by Ganong and Hume (1956) and in rats by Smith (1932) that removal of 70–75 per cent of the pituitary

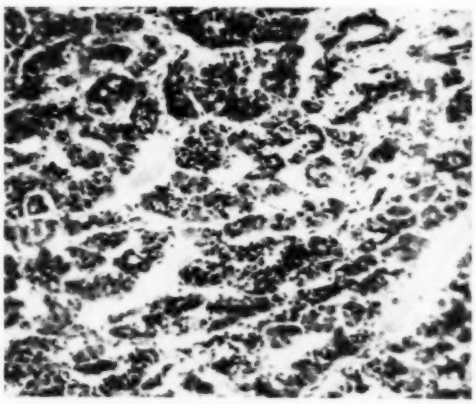

FIG. 144.—*Case* 3. Normal anterior lobe. H. and E. (× 100.)

body results in no detectable endocrine abnormality. The hypophysial vessels of the pituitary stalk have also been shown to have a very strong tendency to regenerate after being divided. This has been demonstrated in several species, in monkeys by Harris and Johnson (1950), in rats by Harris (1949), and in ferrets it was found that it was only possible to prevent regeneration by placing pieces of waxed paper between the cut ends of the stalk (Donovan and Harris, 1954). *Case* 3, in which the pituitary body was examined five months after stalk section and partial removal of the gland, demonstrates that the anterior lobe itself is capable of considerable regeneration.

In rare cases at operation, owing to some anatomical anomaly, it may be found impossible to remove the pituitary body; division of the stalk may then be expected to produce transient improvement. This, as demonstrated by Donovan and Harris, is likely to be more prolonged if a prosthesis is inserted between the cut ends of the stalk to prevent regeneration of the superior hypophysial vessels. However, in most cases the operation of hypophysectomy can be carried out fairly easily with remarkably little post-operative disturbance, the main hazards being due to the administration of a general anæsthetic in very ill patients rather than to the intracranial operation. The operation necessary to expose and divide the pituitary stalk would seem to be little less disturbing, and since its effect is likely to be of short duration only, it is considered that total hypophysectomy should remain the operation of choice.

SUMMARY

The effects of division of the pituitary stalk are described in 3 patients with malignant disease of the breast and prostate.

The pituitary gland was subsequently examined in all cases. In 2 cases only, partial necrosis of the

anterior lobe had occurred, and in the third, the anterior lobe had regenerated.

When ablation of the anterior pituitary is indicated, it is considered that improvement following stalk section is likely to be of short duration only, and that total hypophysectomy is likely to be the more effective.

Acknowledgements.—We wish to thank Dr. F. Kurrein for performing the post-mortem examination in *Case* 3. We are very grateful to Dr. A. L. Woolf for carrying out the histology in all cases and for providing the photomicrographs.

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A CASE OF PRIMARY MALIGNANT MELANOMA OF THE ŒSOPHAGUS

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PRIMARY malignant melanoma of the œsophagus is very rare. The first case was described by Bauer in 1906 and fifty years later Loring and Zeppa (1956), while fully reviewing the literature, were only able to refer to 17 cases, including one of their own. The following is the first case to be reported from the United Kingdom.

CASE REPORT

HISTORY.—The patient (H. S.), a housewife, aged 77, was admitted to Burton General Hospital in October, 1953. There was a history of several months' duration, consisting of increasing dysphagia for solid foods, nausea, flatulence, epigastric pain after meals, and a slight cough with occasional blood-flecked sputum.

On Examination.—Apart from evidence of weight-loss there were no relevant positive findings.

Special Investigations.—The hæmoglobin and white-cell counts were normal and the occult blood-test negative. A barium meal showed a large lobulated tumour in the middle third of the œsophagus (*Fig.* 145). Œsophagoscopy confirmed the presence of the tumour at 25 cm. from the upper incisor teeth and a biopsy was taken from the tumour surface. Histological examination showed "a portion of neurofibroma with some myxomatous change".

The patient was not considered suitable for operation and died at home two weeks later.

POST-MORTEM EXAMINATION.—The body was emaciated. The skin showed no tumours or blemishes.

Alimentary System.—The tongue, mouth, and pharynx were normal. The middle third of the œsophagus was obstructed by a tumour approximately 4 in. × 2 in. × 1 in. attached to the anterior wall by a narrow pedicle about 1 in. long with no obvious invasive characteristics. The stomach showed a small scar of a prepyloric ulcer on the lesser curvature. The remainder of the intestine, the liver, gall-bladder, and spleen were normal.

Endocrine System.—The thyroid, adrenals, pancreas, and pituitary were normal.

Cardiovascular System.—A moderate degree of atheroma, otherwise normal.

Urogenital System.—The kidneys, ureters, bladder, uterus, and ovaries showed no relevant abnormality.

SPECIMEN.—The tumour was found to arise by a narrow stalk, to be lobulated in appearance, and to be in close relation to the aortic arch (*Figs.* 146, 147). On section the centre of the stalk showed a prominent melanotic area which stood out in sharp contrast to the pale, whorled appearance of the main body of the tumour.

FIG. 145.—Radiograph showing the appearance of the tumour following a barium meal.

The upper margin of the melanotic area was sharply defined whereas the lower margin was indistinct and pigment could be seen to extend into the surrounding tumour tissue.

Microscopically the central pigmented area was a typical pleomorphic malignant melanoma (*Fig.* 148). The pale portion of the tumour consisted mainly of interlacing bundles of long-drawn-out spindle cells with elongated nuclei and many intervening collagen fibres (*Fig.* 149). At the upper end of the tumour both these appearances were quite distinct, but at the lower pole islands of pigment-containing melanoma cells were seen together with the spindle-cell areas. Pigmentation was

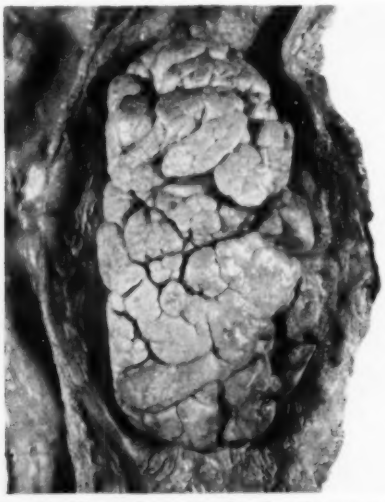

FIG. 146.—The œsophagus opened to show the tumour *in situ* after fixation (*actual size*).

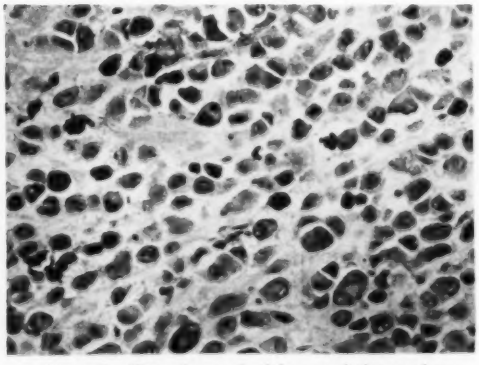

FIG. 148.—Photomicrograph of the central pigmented area showing the presence of melanin and the pleomorphic appearance of the malignant cells. H. and E. (× 300.)

absent from the squamous epithelium covering the tumour, but in the œsophageal lining adjacent to the tumour stalk it was seen in the basal cells of the mucosa and in the histiocytes in the underlying tissue (*Fig.* 150). No junctional activity was found in the sections studied. The œsophageal wall was not infiltrated by the tumour and a neighbouring lymph-node contained no metastases.

The presence of melanin in these sections was demonstrated by silver staining using the Mason-Fontana technique, and by bleaching with hydrogen peroxide. Perl's stain for free iron was negative.

DISCUSSION

It can be seen from the anatomic configuration that the melanotic component of this tumour could not have been detected by superficial biopsy (*Fig.* 147).

FIG. 147.—Longitudinal section of the tumour showing the narrow stalk, melanotic centre, and pale peripheral area (*actual size*).

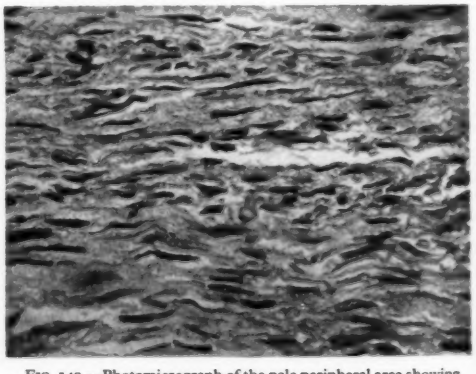

FIG. 149.—Photomicrograph of the pale peripheral area showing the uniform spindle-cell structure. H. and E. (× 300.)

At post mortem the tumour was still regarded as a neurofibroma and its true nature was only revealed later when it had been fixed and cut.

The variation in histological appearances gave rise to some difficulty in diagnosis. An origin from squamous epithelium was considered but the microscopic picture did not support it. The positive staining reaction for melanin, the large amount of pigment present, and the typical cellular appearance established that the central part, at any rate, was a melanoma. The sharp contrast between the cellular,

pleomorphic, pigmented area and the very uniform fasciculated spindle-cell portion by which it was surrounded suggested a possibility of a neurofibroma in addition. The association of neurofibromatoid areas in all types of melanomas is, however, well known, particularly in the blue nævus (Willis, 1953); on the other hand, melanin deposition in the skin occurs in the neurofibromatosis of Von Recklinghausen's disease. The occurrence of neurofibromatoid tissue in melanomas becomes more reasonable

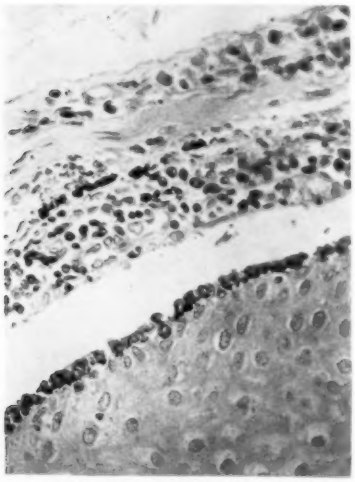

FIG. 150.—Photomicrograph showing pigmentation of the basal cells of the œsophageal mucosa. Pigment-bearing histiocytes are present in the underlying tissues which have become artificially separated in the section. Silver stain. (× 300.)

if the theory that the melanoblasts have their origin in the neural crest is accepted (Masson, 1951). In this case the gross structure of the tumour, the pigmented area almost entirely occupying the stalk, suggested that the whole tumour was a melanoma which had some neurofibroma-like components. Indeed, it would be a most remarkable coincidence if this had been two separate tumours arising together in this manner and situation.

One important feature of this case was the presence of apparently normal pigmented basal cells within the mucosa adjacent to the tumour stalk. Of the previously reported cases, only that of Fowler and Sutherland (1952) has shown a similar finding. In their case the pigmented area was a few centimetres away from the primary tumour. Attempts by these authors and by Becker (1927) to demonstrate melanoblasts and dendritic cells within the human œsophageal mucosa have failed, and Johnson (1910), describing the histology of the developing œsophagus, does not mention their presence. Personal examination of strips of mucosa from 12 post-mortem cases, each sectioned throughout the entire length of the œsophagus, also confirmed the absence of melanin in this situation.

The malignant nature of this tumour was indicated by the cellular irregularity and the degree of mitotic activity, though neither metastases nor infiltration were present. The possibility of secondary melanoma was considered, but these are extremely rare in the œsophagus, only 2 cases being found in the literature (Ranieri, 1941; Spiegelberg, 1895). This, together with the failure to find a primary site or other melanomatous deposits at post-mortem, and the presence of non-malignant pigmented basal cells within the mucosa, strongly suggests a primary origin. In order to conserve the specimen only a few sections were taken and this may account for the failure to find junctional changes; moreover, such changes may be difficult to demonstrate when the epithelium is stretched by the growing tumour (Robertson, 1954).

The absence of melanoblasts in the normal œsophageal mucosa makes it likely that these tumours arise either by metaplasia of normal œsophageal basal epithelial cells (Allen, 1947) or from an area of ectopic melanoblast-containing epithelium included within the œsophagus during development. The occurrence of primary melanomas in other epithelia of endodermal origin such as the small bowel and bronchus has been commented on by Herbut and Manges (1945) and Allen and Spitz (1953). Similar considerations probably apply regarding the origin of these tumours. Careful study of œsophageal material, particularly with regard to melanogenesis, may shed further light on this problem.

SUMMARY

A case of primary melanocarcinoma of the œsophagus has been described and possible modes of origin discussed.

Acknowledgements.—We should like to express our thanks to Professor G. J. Cunningham and to Dr. L. W. Proger for their valuable advice and criticism; to Dr. Ian Mackenzie of Tutbury, whose case this was, for his great interest and help in this investigation; and to the Photographic Department of the Imperial Cancer Research Fund, Lincoln's Inn Fields, who kindly prepared the illustrations.

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CHOLEDOCHODUODENAL FISTULA DUE TO DUODENAL ULCERATION

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SPONTANEOUS internal biliary fistulæ are uncommon, being found in 0·4–4·0 per cent of all operations on the biliary tract (Noskin, Strauss, and Strauss, 1949). The majority of such fistulæ are due to gall-stones ulcerating from the gall-bladder into the duodenum. Only 6 per cent are caused by duodenal ulceration, but in these cases the fistulæ are usually into the common bile-duct (Waggoner and LeMone, 1949). Thirty-five examples of this type of choledochoduodenal fistula have been reported. Only a few of the patients had presented with symptoms of cholangitis, and it was usually impossible to demonstrate the fistula at operation (Cogbill and Roth, 1953). The three cases described below were all treated within a period of eighteen months and in each case the fistulous communication was clearly seen at the time of operation.

FIG. 151.—*Case* 1. Pre-operative intravenous cholangiogram showing gas but no radio-opaque dye in the biliary ducts (contrast increased).

CASE REPORTS

Case 1.—A slightly jaundiced man, aged 77 years, was admitted to hospital on June 27, 1955. For thirty years he had had symptoms of duodenal ulceration, with severe pain coming on several hours after food and being relieved by taking sodium bicarbonate. During the last three years he had had at least eight attacks of jaundice, associated with right upper abdominal pain and rigors, and these attacks were becoming more frequent. Apart from the slight icteric tinge, and some evidence of weight-loss, physical examination revealed no abnormality. His serum bilirubin was 1·3 mg. per cent (normal=0·1–0·5 mg.), and his serum alkaline phosphatase 20 K.A. units per cent (normal=4·5–9·5 K.A. units). An intravenous cholangiogram was performed on June 30, 1955, but it failed to demonstrate the biliary passages. However, gas was seen to be present in the hepatic and common bile-ducts (*Fig.* 151). No calculi were demonstrated. At operation on July 5, no gall-stones could be felt in the biliary tract, but there was a firm mass, 2·5 cm. in diameter, behind and above the first part of the duodenum. The anterior wall of the duodenum was opened revealing a posterior wall ulcer, from the centre of which bile was exuding. A Polya-type of partial gastrectomy was then carried out, the duodenum being closed without much difficulty proximal to the ulcer.

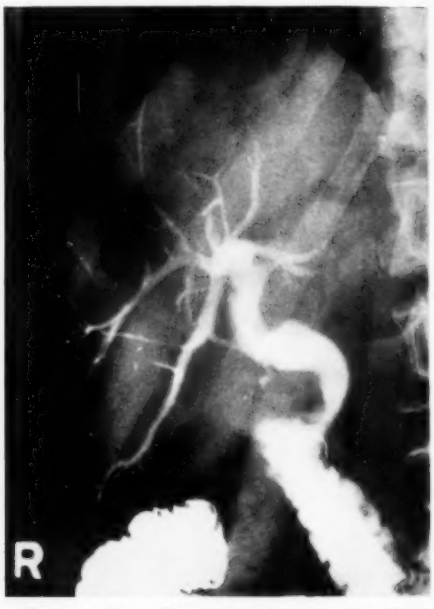

FIG. 152.—*Case* 1. Post-operative barium meal showing the main bile-ducts filled with barium which has passed through the persistent choledochoduodenal fistula.

Recovery was satisfactory. Two years later the patient was keeping very well, had had no further symptoms, and had gained over 1½ stone (10 kg.) in weight. His serum bilirubin was 0·4 mg. per cent, but on radiography, barium still passed readily into the biliary ducts, apparently through the choledochoduodenal fistula (*Fig.* 152).

Case 2.—A man, aged 46 years, was admitted on Nov. 9, 1956. He gave a history of duodenal ulceration of twenty years' duration, and had had a hæmatemesis eleven years previously. Barium meal examination in 1940 and in 1955 had shown a deformed duodenal cap. During the first nine months of 1956 the patient's symptoms had become increasingly severe in spite of medical treatment at home. He was again referred to hospital, but before he was seen in the Out-patient Department on Oct. 1, 1956, all his symptoms had suddenly disappeared. However, a further barium meal examination was carried out, and showed barium flowing freely into the common bile-duct (*Fig.* 153). Clinically there was no evidence of jaundice, but in view of the risk of cholangitis operation was advised. On Nov. 15, a subtotal Polya-type of gastrectomy was performed. The stomach was found to be dilated and there was marked stenosis of the juxtapyloric portion of the duodenum. Just beyond the

stenosed area a healed posterior wall ulcer could be palpated and when the duodenum was transected at its narrowest point, the edge of this ulcer could be seen. In the depths of the healed ulcer crater an opening about

Six months later the patient was very well. On X-ray examination barium could not be induced to enter the afferent loop of the gastrojejunal anastomosis, but gas could be seen in the biliary tree (*Fig.* 156).

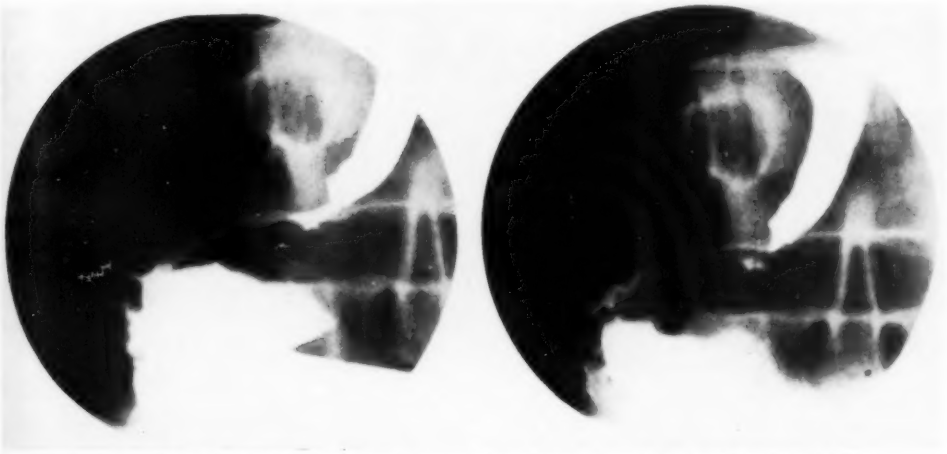

FIG. 153.—*Case* 2. Pre-operative barium meal showing reflux of barium through the choledochoduodenal fistula.

0·5 cm. in diameter was visible, and a probe passed readily through it into the common duct; the probe could not, however, be passed down towards the ampulla of Vater. It was possible to close the duodenal stump without occluding the fistulous opening. No calculi were palpable in the gall-bladder or common duct.

The patient's post-operative course was straightforward and when seen on July 4, 1957, he was symptom-free and had a good appetite. A barium meal examination, however, still showed a reflux of barium into the biliary tract (*Fig.* 154).

Case 3.—A woman, aged 62 years, was first seen at hospital on May 4, 1956. She stated that for fifteen years she had suffered from recurrent attacks of epigastric pain. A barium meal examination at another hospital in 1954 had shown a deformed duodenal cap consistent with the presence of an ulcer. Recently the attacks of pain had become more frequent and the patient vomited occasionally; she had had one small hæmatemesis. A barium meal revealed a very small deformed duodenal cap, with marked initial delay in gastric emptying.

The patient was treated medically but her symptoms persisted. A further barium examination was therefore carried out on Nov. 16, 1956. Barium was seen to pass into the common bile-duct (*Fig.* 155). An intravenous cholangiogram showed air but no contrast medium in the biliary passages. The serum bilirubin level was less than 0·5 mg. per cent.

At operation on Feb. 1, 1957, the pylorus and adjacent duodenum were found to be about 1 cm. in diameter. After the duodenum had been transected, its anterior wall was opened longitudinally in order to expose a posterior wall ulcer situated 3 cm. beyond the pylorus. A short fistulous track from the common bile-duct opened into the ulcer crater. A probe passed readily through it up into the hepatic ducts, but would not pass in a downwards direction. Closure of the duodenal stump proved rather difficult, and after completing a Polya-Hofmeister gastrectomy the previously normal gall-bladder was noticed to be distended. In case the duodenal closure had obstructed the flow of bile through the fistula, the gall-bladder was drained externally for 6 weeks.

FIG. 154.—*Case* 2. Post-operative barium meal. The persistence of the fistula after Polya gastrectomy is clearly demonstrated.

COMMENT

The rarity of spontaneous choledochoduodenal fistulæ seems a little surprising in view of the frequency of duodenal ulceration, and of the proximity of the common bile-duct to the first part of the duodenum. Nissen (1945), however, has shown that the common duct mostly passes behind the duodenum

at a point lateral to the usual site of ulceration, and is frequently separated from it by the superior edge of the pancreas. In all three cases described above, the fistulæ were only 2–3 mm. long, so that in none of them could there have been a protective layer of pancreatic tissue intervening between the ulcer base and subjacent duct.

The first report of a duodenal ulcer penetrating into the biliary tract was that of Long (1840), in the paper in which he described peptic ulceration following burns. In the second half of the last century there were several reports (reviewed by Moynihan, 1910) of duodenal ulcers obstructing the common bile-duct, and causing cholangitis and jaundice. As in recent times it has often been found difficult or impossible to demonstrate a radiologically-proven fistula at operation, some of these early cases may in fact have been examples of choledochoduodenal fistula. The condition may not be as rare as the scarcity of reports would suggest.

The nature of the symptoms resulting from a penetrating duodenal ulcer must also be remembered. The symptoms tend to be resistant to medical treatment, and pain is severe and unremitting, so that many patients may seek surgical relief before a fistula has time to develop.

A possible explanation for the infrequent recognition of an established fistula is that since the ulcer is bathed in alkaline bile the ulcer symptoms rapidly abate. Consequently medical advice is not sought. It seems likely that in *Case* 2 the sudden disappearance of symptoms was due to the perforation of the ulcer into the common bile-duct. With the distal part of the common duct obstructed the fistula might persist indefinitely. It is known that patients with internal biliary fistulæ may enjoy good health for a long time (Carlson, Gates, and Novacovitch, 1955) and cholangitis is rare with a choledochoduodenal fistula (Cogbill and Roth, 1953).

Barium meal examination appears to be the most likely method of detecting a choledochoduodenal fistula (Garland and Brown, 1942; Waggoner and LeMone, 1949). The radiological features of the condition have recently been described by Heron (1958). Clinically there are no characteristic symptoms, apart from the symptom-sequences exemplified in *Cases* 1 and 2, namely, a long history of duodenal ulceration followed, rarely, by attacks of cholangitis, or by the sudden disappearance of all symptoms.

Good results have followed treatment by subtotal gastrectomy of the Polya-type (Cogbill and Roth; Epperson and Walters, 1953). With adequate gastric resection recurrence of ulceration is prevented and the bile drains into a defunctioned limb of bowel. The fistula, however, persists, but the by-passing of the duodenum evidently prevents the development of recurrence of cholangitis. Attempts to demonstrate the fistula at operation should be kept to a minimum, otherwise it may be difficult to close the duodenal stump without at the same time obstructing the flow of bile. Rarely, when the orifice of the fistula lies close to the usual line of duodenal transection, it may be necessary either to slit the septum between the fistula and the duodenum distally (Yon and Bell, 1953) or else to use Bancroft's procedure of dividing the pyloric antrum and then closing the distal part after removing its mucosa (Macumber and Stoll, 1954).

FIG. 155.—*Case* 3. Pre-operative barium meal. The biliary tree has filled with barium through the fistula situated beyond the stenosed pylorus.

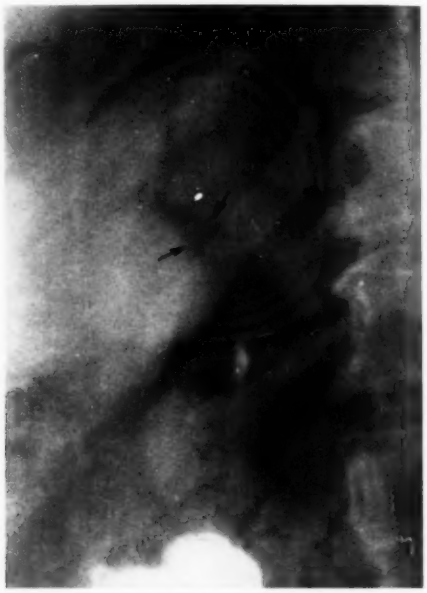

FIG. 156.—*Case* 3. Post-operative barium meal. Gas is present in the main bile-ducts, but barium would not enter the afferent loop of the Polya-Hofmeister gastrectomy.

SUMMARY

Three examples of choledochoduodenal fistula due to peptic ulceration are described. All were detected on radiological examination of the upper abdomen. They were treated successfully by Polya-type subtotal gastrectomies, but the fistulæ persisted.

Addendum.—Since the submission of this paper for publication a fourth patient has been treated by Polya gastrectomy. He had had a 40-years' history suggestive of duodenal ulceration and was admitted with pyloric obstruction. A barium meal outlined the lower part of the biliary tract. At operation there was an inflammatory mass involving the first part of the duodenum. There appeared to be penetrating ulcers on both the anterior and posterior walls. Because of difficulty of access it was not possible fully to explore the fistula to find out if the lower part of the common bile-duct was occluded as in *Cases* 2 and 3. Bancroft's procedure was used to close the duodenal stump.

Acknowledgements.—It is a pleasure to thank Mr. M. Lavery, Mr. G. D. F. McFadden, Professor H. W. Rodgers, and Mr. S. A. Vincent for their help and advice and for permission to publish this report.

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LEIOMYOMA OF THE DUODENUM

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LEIOMYOMA of the duodenum is the lesion in 5 per cent of smooth muscle tumours of the gastro-intestinal tract and retroperitoneal tissues (Golden and Stout, 1941). It is usually found in the first and second parts, but is uncommon in the third part. The case reported here is of a leiomyoma arising in the third part of the duodenum.

CASE REPORT

A man, aged 43, was admitted on Oct. 6, 1955, complaining of vague dull pain in the right side of the lower abdomen which had been present for three days. There was an associated mild frequency of micturition and malaise. He had lost his appetite and was constipated. Prior to this he had been in good health, apart from an appendicectomy in 1938, dysentery in North Africa in 1944, epidemic jaundice in Italy in 1944, and again dysentery in India in 1952. The family history did not reveal anything of significance. On the morning of his admission he passed a loose tarry stool.

ON EXAMINATION.—The patient was obese, had a temperature of 102° F., and his blood-pressure was 150/90. The right side of the abdomen was generally tender, but there was no palpable mass. On rectal examination, black fæces were found on the examining finger, but a mass was not felt. The central nervous system was normal on routine examination, and it was noted that there was no apparent visual disability (*see below*).

Later, on the day of admission, the patient passed another stool containing a fair amount of dark red blood. After forty-eight hours his temperature returned to normal. Two weeks later he said that he passed a bright red bloody stool, but this was not confirmed by observation of the specimen.

Radiological Examination.—The whole of the alimentary tract was carefully visualized with barium. A filling defect was found in the lumen of the third part of the duodenum which measured 3 cm. in its long axis. The defect did not appear to have the normal mucosal pattern over its surface, and had a fairly sharp rounded

FIG. 157.—The pylorus, first, second, and third parts of the duodenum outlined by barium. In the third part of the duodenum a smooth filling defect with a sharp border can be seen. This defect represents the tongue-like process.

border; it was not causing any intestinal obstruction (*Fig.* 157). There was no radiological evidence of any soft tissue mass associated with it, although the psoas shadow on the right side, while not obliterated, seemed somewhat denser in most films compared with the other side.

An excretion pyelogram was then performed. The preliminary film confirmed the increased density of the right psoas muscle which had been previously noted. The shadow of the right ureter was found to be displaced laterally opposite the bodies of the second and third lumbar vertebræ, returning abruptly to its normal position opposite the fourth lumbar vertebra. There was nothing characteristic about the displaced ureter to suggest the nature of the displacing mass.

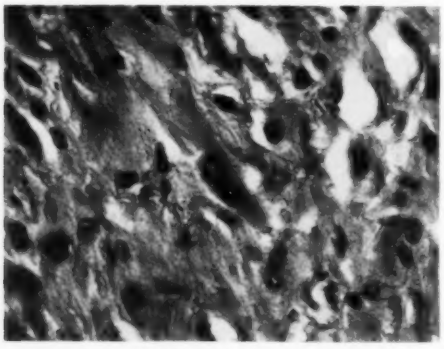

FIG. 158.—The highly cellular tumour composed of plump spindle-shaped cells with abundant fibrillar cytoplasm and blunt ovoid nuclei.

Keeping in mind the possibility of a smooth muscle tumour in such a case of obscure melæna (Golden and Stout, 1941), this, combined with abdominal pain and radiological evidence of a mass in the lumen of the duodenum which extended into the retroperitoneal space, prompted a diagnosis of leiomyoma, and excision of the tumour was advised.

AT OPERATION.—On Oct. 28, 1955, a leiomyoma of the third part of the duodenum was found. It presented as a mass in the retroperitoneal space, medial to the ascending colon, and below the transverse mesocolon. The posterior layer of the peritoneum covering the tumour was intact, but the bluish-red colour of the tumour could be seen through it. The right half of the colon was mobilized and displaced medially, exposing the tumour and the third part of the duodenum. The right ureter was found to be firmly adherent to the lateral and posterior surface of the tumour and had to be dissected off by sharp dissection. The right colic vessels seemed to pass through the tumour and had to be divided medial and lateral to the mass; the marginal artery of the colon proved adequate to maintain the blood-supply to the ascending colon (Griffiths, 1956). The third part of the duodenum and the tumour were mobilized. The tumour had excavated a bed for itself in the psoas muscle and was firmly adherent to it. The duodenum was divided 2·5 cm. proximal and distal to the tumour, excising the tumour together with a segment of duodenum approximately 7 cm. long. The distal end of the duodenum was closed and the proximal end was anastomosed, end-to-side, to a loop of jejunum about 25 cm. distal to the duodenojejunal flexure. The anastomosis was extraperitonealized and the retroperitoneal space was drained down to the anastomosis.

POST-OPERATIVE COURSE.—The patient developed an atelectasis of the right lower lobe of the lung which responded to conservative treatment in a few days. When he had recovered from his operation he began to complain of dimness of vision. He was examined by the ophthalmologist, whilst still in hospital, and was again seen as an out-patient two months later on Dec. 2, 1955, when a diagnosis of presbyopia was made. On Dec. 30, 1955, he was followed up again in the eye clinic and was found to have a left homonomous hemianopia with macular sparing. This complication has remained unchanged to date, but he compensates well for this disability. The patient was discharged from hospital on Nov. 9, 1955. A follow-up examination fourteen months later did not show any evidence of recurrence of the tumour, locally or at a distance.

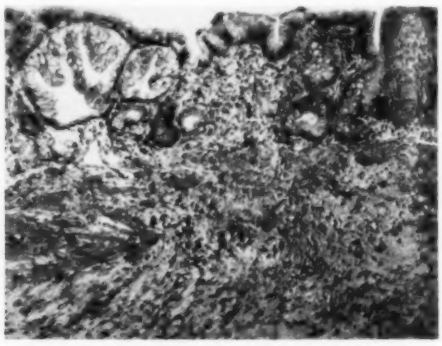

FIG. 159.—The degree of cellularity, whorled pattern, and absence of palisading are well demonstrated. The duodenal mucosa is intact, is not invaded, and forms a limiting membrane for the tumour on this surface. The submucosa and muscular coats have been completely replaced by tumour tissue. No hæmorrhages are seen under the mucosa.

GROSS DESCRIPTION.—The specimen weighed 85 g. and comprised a 6-cm. segment of duodenum, attached to which was a nodular roughly spherical mass measuring 5 cm. in diameter. The cut surface was coarsely lobulated, grey-white and opaque, and showed irregular areas of softening and reddish discoloration. Other areas showed foci of brownish discoloration. The consistency was firm and fairly resilient. The mass extended into the lumen of the duodenum where it formed a freely mobile tongue-like process, the surface of which was covered by intact duodenal mucosa. At the tip of this process the mucosa was deeply pitted, but no break in the mucosa could be identified. Careful examination of other irregularities on the surface of this process disclosed no visible bleeding point.

MICROSCOPY.—The tumour was highly cellular and was composed of plump spindle-shaped cells with abundant fibrillar cytoplasm and blunt ovoid nuclei. These cells were arranged in a strikingly whorled pattern without palisading. The nuclei contained finely divided chromatin and one or more clearly defined but relatively small nucleoli. In some areas there was an appreciable variability in the size of the nuclei. Occasional relatively large multinucleated cells were found, but an exhaustive search for mitotic figures was fruitless (*Fig.* 158). No microscopic foci of ulceration and no hæmorrhages were detected in the overlying duodenal mucosa (*Fig.* 159). Numerous venule-sized, thin-walled, vascular channels were uniformly interspersed throughout the tumour tissue. In the intraluminal portions of the tumour extensive areas of recent and organizing hæmorrhage were present. These were associated with coagulation necrosis, with secondary inflammatory changes, and with zones of dense hyalinization, but were not accompanied by signs of active growth. The staining affinity of the cytoplasm of the tumour cells was that of smooth muscle. A fine meshwork of collagenous and reticulum

fibres separated the tumour cells from one another. Cell clusters that were sectioned transversely appeared to be composed of ovoid cells with highly granular cytoplasm resembling those of granular-celled myoblastomas. Among the consultant pathologists who examined the microscopic slides, a minority favoured a diagnosis of leiomyosarcoma. After a thorough review of the case, it was decided that evidence for malignancy was inconclusive, and a diagnosis of leiomyoma was finally reached.

DISCUSSION

A leiomyoma arising from the duodenum usually simulates the symptoms of peptic ulceration and has a long history. The second part of the duodenum is the commonest site of origin in at least 50 per cent of cases. In some, because of its large size, the tumour is responsible for constipation or diarrhœa, or both, by compressing the overlying transverse or ascending colon. Sometimes it partially occludes the inferior vena cava or the superior mesenteric vessels, and death due to pulmonary embolism or to thrombosis is common. A palpable tumour is present in only 25 per cent of the cases. Perforation of a degenerating duodenal leiomyoma into the peritoneal cavity is somewhat more frequent than with gastric cases (Golden and Stout, 1941). The tumour reported here, however, arose from the third part and presented with a remarkably short history of abdominal pain, disturbance of micturition, and melæna. A correct pre-operative diagnosis was made and the case successfully treated.

It is presumed that the relatively acute onset of the abdominal symptoms was due to hæmorrhage into the tumour, with œdema and congestion of the adjacent ureter causing the frequency of micturition. As the patient had no anæmia prior to his operation, the bleeding episodes into the alimentary tract must have been minimal, the blood coming from congestion of the overlying and intact duodenal mucosa. It should be emphasized here that only 50–80 c.c. of blood in the alimentary tract is sufficient to cause a tarry stool (Daniel and Egan, 1939). In this case, the tumour did not follow a common pattern, with a fairly long history of melæna and the formation of a diverticulum.

The case reported here also serves as an example of the value of careful barium-meal examination of the small intestine in cases of melæna (*Fig.* 157). Starr and Dockerty (1955) emphasize that this procedure is a significant aid to the pre-operative diagnosis. Of 30 cases reported by them which were proved at operation to be smooth muscle tumours of the small intestine, the radiologist had been able to demonstrate the tumour in 23 cases, and in 7 of the latter there was enough radiological evidence for the pathological diagnosis to be made.

The cause of the left homonomous hemianopia is presumed to have been due to a vascular accident in the anterior part of the optic radiations on the right side. As this lesion did not appear to reach its maximum for some days post-operatively, the vascular accident is thought to have been a thrombosis associated with mild hypertension. It was noted in a study of the literature on leiomyomata of the alimentary tract that there was a peculiarly high incidence of various post-operative complications amongst this type of case, and no explanation is offered to account for this.

The specimen is an excellent example of the dumb-bell shape which some of these tumours may assume. Usually they are intramural, exocentric, or endocentric in position. As exemplified by this case, the histological differentiation of benign from malignant smooth muscle tumours of the small intestine may be difficult, controversial, and in a small proportion of cases unreliable (Ackerman, 1953). Here, the relatively small size of the tumour and its apparent inactivity, as emphasized by the lack of mitotic figures, favoured a benign growth. However, it must be admitted that the tumour was highly cellular, showing many atypical nuclei. Lahey and Colcock (1940) reported that these tumours look microscopically much less benign than external appearances and future behaviour would warrant. Fortunately, the type of malignant degeneration which occurs in these tumours is usually of a low grade, and long survival can be expected in most cases.

SUMMARY

1. A case of leiomyoma of the third part of the duodenum is reported.

2. A correct pre-operative diagnosis was made following the radiographic demonstration of the tumour.

3. Leiomyoma must always be considered in the differential diagnosis of melæna.

4. The histological differentiation of benign from malignant gastro-intestinal leiomyomata is frequently difficult and controverisal. If malignant degeneration is found, it is of such a low grade that long survival can be expected.

5. Abdominal pain and frequency of micturition are added to the list of reported symptoms of a duodenal leiomyoma.

My thanks are due to Dr. J. Campbell of the University of Ottawa for the pathological report and for *Figs.* 158 and 159; to the Royal Canadian Air Force Photographic Establishment for the preparation of *Fig.* 157, and to Wing Commander W. L. Orr of the Royal Canadian Air Force Hospital, Rockcliffe, for the radiograph (*Fig.* 157).

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MOLTEN METAL BURNS OF THE LOWER EXTREMITIES

By R. G. MAIN, Falkirk, Scotland

In the area served by Falkirk and District Royal Infirmary, one of the main industries is the 'light castings' industry, and as a consequence, a relatively large number of foundries is concentrated in the district. The process is, in many cases, not highly mechanized and depends upon the traditional skill of the 'moulders'. It involves transference of molten metal from the furnace to various types of pre-formed mould. This mould is made of sand rammed hard, in which is a cavity representing the shape of the required casting. It is usually contained in a sectional iron box. The molten metal is collected from the furnace in a large, wheeled, metal container ('bogie-ladle'), from which it is dispensed into smaller, long-handled hand ladles. These ladles are carried by the individual moulders and the metal is poured from them into the mould. When cooling and solidification have taken place, the sectional box is taken apart and the casting knocked out of the sand (*Figs.* 160–163).

Fig. 160.—Molten iron pouring into bogie-ladle from cupola. *Note*: The iron is pouring down a runner.

Fig. 161.—Moulder pushing bogie-ladle.

From this description the process perhaps sounds delightfully simple, but, in fact, involves a very high degree of skill and dexterity. Both management and employees are acutely conscious of the dangers of the occupation, and much time and thought are given to accident prevention and first aid. Well-equipped ambulance rooms are maintained, usually attended by a full-time works nurse and visited by a medical officer. The foundries are proud of their low accident rates, and while one finds them eager to co-operate in every way, it behoves any investigator to tread with a degree of tact and humility in face of the fine traditions of this great industry. It is interesting that the well-known Carron oil, which derives its name from one of the oldest of the companies, is still bought and used as a sovereign palliative for burns of all kinds nearly 200 years after it was first prescribed!

(Very old prescriptions for Carron oil are still to be found in the premises of R. Gordon Drummond, Pharmacists, in Falkirk High Street. As dispensed, it consisted, in the earliest days, of a mixture of equal parts of linseed oil and lime water. A later improved formula contains ten parts lime water, nine parts olive-oil, and one part eucalyptus oil.)

In spite of the precautions taken, a number of burning accidents occur:—

1. Many patients are treated in the works ambulance rooms without significant loss of working time.
2. Those burns which are more severe but which do not require hospitalization are treated in the casualty department of the infirmary and by the patients' own family doctors.
3. A number of the burns, however, may be classed as 'severe' and these require admission to hospital for surgical treatment.

It is with the last group that this short paper deals, and, for its purpose, the records of 37 in-patients have

been extracted covering the period December, 1950, to April, 1957 (*Table I*).

From a study of the records, the following facts become apparent:—

1. *The burns, on the whole, are not extensive in surface area.* Secondary 'burns shock' is not a problem; fluid loss or shift is slight; intravenous infusion is only rarely required.

2. *The lower extremities are almost exclusively involved.* Burning is virtually confined to the foot and ankle; the left lower limb has been involved more than twice as often as the right (73 per cent) (*Fig.* 164).

We are fortunate in having within easy reach at Bangour Hospital a most efficient and co-operative plastic surgery unit which accepts from us cases of an unusually extensive nature, and cases likely to require full-thickness grafts or cross-leg flaps, e.g., with loss of skin over tendo Achillis. Five cases in this group have been transferred. When the remaining 32 cases are considered, it is seen that—

3. *Full-thickness skin loss has occurred in* 29 (90·6 *per cent*) and skin-grafting has been carried out in 24 cases.

FIG. 163.—Moulders pouring the metal into a mould.

THE BURNS

In the earliest stages the burns (*Fig.* 165) are extremely painful, but when seen in hospital after a few hours many are quite painless. The episode, in most cases, causes acute anxiety, but overt primary 'neurogenic' shock is not often seen in hospital. The appearance of the burn is often quite characteristic. Erythema and vesication are sometimes seen, but in the typical full-thickness burn there is a localized area which may not differ greatly from the surrounding normal skin to the inexperienced observer, and which is often misinterpreted by the house-surgeon in the casualty department as indicating a superficial burn. (It is necessary to warn each succeeding generation of casualty officers of this point in order to secure timely admission to the wards.) With repeated observation of such burns, the following features are noted:—

FIG. 162.—Moulders filling hand-ladle from bogie-ladle.

1. The area is white and relatively avascular.
2. It lacks the moisture and lustre of normal skin.
3. The central area often has a light brown tinge which is the result of charring of the skin (sometimes mistakenly interpreted as contamination from charred clothing).
4. After a few hours there may be a narrow margin of erythema between the burn and the surrounding normal skin.
5. The area is often hypo-algesic to pin-prick. (This has not proved to be a reliable sign of full-thickness burning and its elicitation is not encouraged.)
6. The burns are always well-delineated and in shape are roughly circular or scalloped.

MECHANISM OF BURNING

It will be seen that the sites of burning fall fairly uniformly within the 'boot' area. Burns of the legs are relatively quite uncommon. The high proportion of full-thickness burning is due to the fact that the hot molten metal runs down into the boot and is trapped in contact with the skin during the time in which the boot is feverishly removed. (It is interesting that in one recent case in which partial-thickness loss only occurred, the moulder happened to be standing beside a bucket of cold water into which he at once plunged his booted foot.)

Table I.—THIRTY-SEVEN CASES OF MOLTEN METAL BURNS TREATED IN HOSPITAL

Case No.	Site	Depth		Side		Early Excision and Grafting	Delayed Grafting	No. of Days in Hospital	Transfer to Plastic Unit
		Partial Thickness	Full Thickness	Right	Left				
1	Below lateral malleolus	+			+			5	
2	Medial border of foot	+			+			8	
3	Both borders of foot, sole and heel	+		+				18	
4	Large area over t. Achillis		+		+				+
5	Both wrists. Left foot over t. Achillis and anterior ankle	+	+		+				+
6	Anterior and posterior ankle over t. Achillis		+		+				+
7	Both hands and left leg. Extensive		+		+				+
8	Sole and heel		+		+				+
9	Plantar surface of foot over transverse arch		+	+		1 in. diameter. No graft. Treated as out-patient			
10	Lateral surface of foot		+	+		Discharged to out-patients' department at own request. No graft		33	
11	Heel		+	+		Not extensive. No graft. Not healed on discharge		37	
12	Plantar aspect of toes and transverse arch		+	+		Not extensive. No graft		63	
13	Below lateral malleolus		+		+	24 hr. old. Refused graft		69	
14	Outer border of foot		+		+		+ (after 22 d.)	29	
15	Small areas of foot		+		+		+ (after 12–26 d.)	36	
16	Dorsum of foot and ankle. Extensive		+		+		+ (after 18 d.)	42	
17	Below medial malleolus		+		+		+ (after 24 d.)	44	
18	Below medial malleolus		+		+		+ (after 29 d.)	44	
19	Below lateral malleolus		+		+		+ (after 24 d.)	45	
20	Below lateral malleolus		+		+		+ (after 33 d.)	47	
21	Sole		+	+			+ (after 13 d.)	51	
22	Dorsum, sole, and heel		+		+		+ (after 23 d.)	51	
23	Ankle, lateral malleolus		+		+		+ (after 26 d.)	53	
24	Lateral border of foot and below medial malleolus		+		+		+ (after 33 d.)	55	
25	Sole and lateral border of foot		+	+			+ (after 30 d.)	59	
26	Ankle, medial and lateral		+		+		+ (after 37 d.)	65	
27	Lateral side of ankle, medial border of foot		+		+		+ (after 31 d.)	87	
28	Dorsum		+	+		+ (within 24 hr.)		16	
29	Dorsolateral aspect of foot		+		+	+ (within 24 hr.)		17	
30	Anterior ankle, lateral border of foot		+		+	+ (after 2 d.)		19	
31	Below medial malleolus		+	+		+ (within 24 hr.)		21	
32	Anterior and posterior to medial malleolus		+	+		+ (within 24 hr.)		25	
33	Anterior ankle. Dorsum and sole of foot		+		+	+ (within 24 hr.)		26	
34	Dorsolateral aspect of foot		+		+	+ (within 24 hr.)		28	
35	Lateral aspect of ankle		+		+	+ (within 24 hr.)		30	
36	Below and posterior to medial malleolus		+		+	+ (within 24 hr.)	70 per cent 'take'. Pinch grafts after 20 d.	32	
37	Lateral aspect and sole of foot		+		+	+ (within 48 hr.)		37	

Average 50·6 d.

Average 25·1 d.

In order to make a more detailed study of the mechanism, visits have been paid to selected foundries and the moulders and staff have been interviewed and observed at work. The following points have emerged.

Sparks from the molten metal cause minor burns of the exposed parts but do not penetrate or adhere to the clothing to any significant extent since they cool rapidly. Splashes of molten metal on the exposed parts tend to cause partial-thickness burns. The commonest mechanism of severe burning, however, is apparently the stubbing of the toes while carrying a full hand-ladle, or the striking of the ladle against some projecting object. Since the ladle is carried as shown in *Figs.* 166 and 167, the metal is spilled on the legs and since the *right*-handed moulder usually carries the ladle close to his *left* leg, the *left* ankle and foot are more commonly involved (p. 131). At first it seems likely that metal spilled in this way runs down the surface of the trouser legs and is trapped by the open 'upper' of the boot (shoes are strictly forbidden and most moulders wear special boots in which an external tongue covers the lace-holes to prevent the access of metal by this route (*Fig.* 168)). This may happen in certain unusual postures, but further consideration makes it seem unlikely in most cases, because the trousers are worn long and tend to overhang the uppers even with the knee flexed. Some moulders were convinced that the metal at once burned a hole in the trouser leg and, penetrating the cloth, ran down inside the garment and was guided into the boot by the projecting upper. Since this suggestion was made, the trouser legs have been examined in several cases of foot burning and have all been found to have recently burned holes in likely sites. One moulder who habitually wore the trousers outside the upper garments and supported them with braces so that the waist-band was loose, actually maintained that on several occasions splashes of metal had entered the inner aspect of the trousers at the waist and had been felt to run down the entire length of the leg and escape at the ankle without causing any burning whatever!

Sometimes the burns are the result of the bursting of a 'box' as it is filled with molten metal.

Occasionally very severe burns have been caused by moulders being trapped in a pool of molten metal when a large leak has occurred, e.g., by the giving way of the plug controlling the furnace spout.

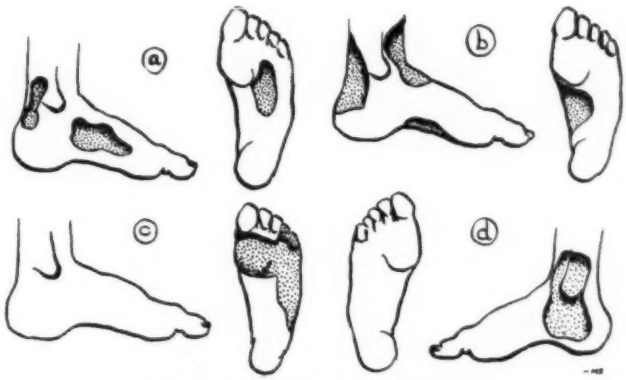

FIG. 164.—Distribution of four typical burns.

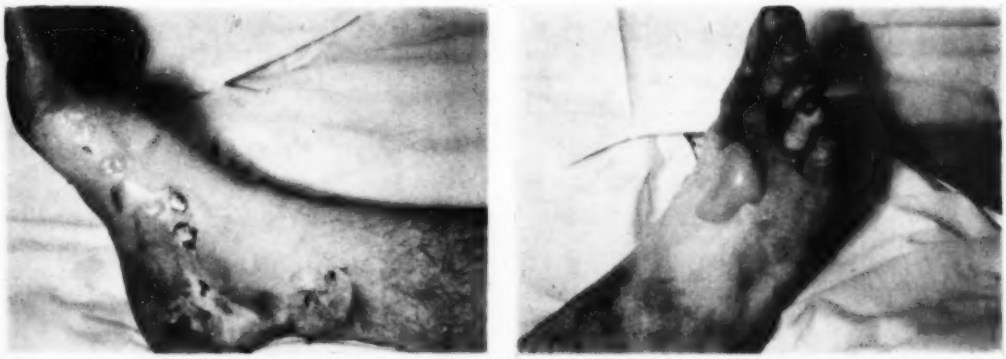

FIG. 165.—Very severe molten metal burn of foot. Full-thickness skin burn from malleoli distally, showing avascular area, vesication, and charring, before any treatment.

PROPHYLAXIS

From observation and discussion it would seem that the following points are relevant to the prevention of these burns.

1. The elimination of projections in the path of the operator and the maintenance of a clean, smooth, floor free of unnecessary rails, tools, and extraneous pieces of metal and wood.

2. The encouragement of continuous caution and a sense of pride in a low accident-rate.

In the foundries visited, a high standard in respect of the above two points has been found and, indeed, it is difficult to see how the present standard can be improved upon, for the accident-rate is really surprisingly low. In some foundries there has not been a severe burn for periods of two to three years and yet enthusiasm is maintained.

FIG. 166.—Right-handed moulder carrying hand-ladle.

FIG. 167.—Left-handed moulder carrying hand-ladle.

FIG. 168.—Protective boot.

FIG. 169.—Safety legging as manufactured by Safety Products Ltd., Redhill, Surrey.

3. The wearing of suitable clothing. It seems to the writer that in this lies the main field for improvement and that, by suitable measures, the severe type of burn could be virtually eliminated.

It was formerly widely held that the metal entered the boot through the lace-holes and around the tongue, but even with the protective boots worn, the burns still occur. As described in the section 'Mechanism of Burning' it would seem that the metal commonly strikes the leg below the knee, probably burns its way through the trouser cloth, or else enters above or below the trousers, and runs down to be guided into the boot by the upper. What is required is a fireproof legging, so designed as to guide the metal over the boot. It must be light, cool, closely-fitting, easily applied, and have a quick-release mechanism. Leggings designed for this purpose are seen in *Fig.* 169. If the designs could be agreed with the employees' representatives and their use made compulsory, it seems likely that a drastic reduction in morbidity could be effected. The outer clothing should preferably be a one-piece garment, or alternatively the upper garments should be worn outside the lower.

TREATMENT

The full-thickness burn has, by tradition, been treated conservatively in the initial stages. Systemic antibiotics have been given prophylactically or therapeutically in the course of treatment. After some days a dark adherent slough forms, which separates only slowly. If it is allowed to separate spontaneously or with the help of eusol dressings, many weeks may elapse before the surface is suitable for skin-grafting and, in some cases, irregular epithelialization proceeds in parallel with the separation of a reticular slough, precluding grafting, and leaving an irregular scar subject to keloid formation. In the past it has been the practice to excise the black sloughs when they have begun to separate and then to prepare the surface for grafting with eusol or antibiotic creams according to any bacterial flora present. From the table it will be seen that this has allowed grafting after an average period of 26 days from the date of burning and that the average period of hospitalization has been 50·6 days.

Taking stock of these burns, the writer noted that almost all required skin-grafting, and with increasing experience of the type of burn, it was found possible to recognize the actual or potential full-thickness loss on admission. A change of policy was therefore instituted, and the burns were excised and skin-grafted (or if possible the defect sutured) as an emergency measure within twenty-four hours of burning. With this, it will be seen from the table that the average period of hospitalization is now 25·1 days. When the burns are excised there is a tendency to gaping and the defect is somewhat larger than expected. It can often be reduced in size by undercutting or local rotation and partial suture. The resultant scars are adequately strong and relatively free from keloid formation, sepsis being minimal. Split-skin grafts cut from the thigh by Humby knife are used.

The second method would therefore appear to be the treatment of choice.

Note.—The approximate average surface area of the burns has been calculated. It is practically the same in both groups. As a rule, burns smaller than 1 in. in diameter have been treated expectantly in the out-patient department.

SUMMARY

A series of molten metal burns of the lower extremities treated at Falkirk and District Royal Infirmary from 1951 to 1957 is described and the mechanism of production, prophylaxis, and treatment are discussed.

It is suggested that the main necessity in prevention is the compulsory wearing of suitable protective clothing and leggings.

The institution of the technique of immediate excision and skin-grafting of full-thickness burns has reduced the average period of hospitalization by one half.

Acknowledgements.—I am very pleased to record my grateful thanks for much help willingly given in the preparation of this paper to Dr. D. F. Nicholson, Medical Adviser, Mr. E. J. Leaver, Managing Director, and Mr. William Brown, all of Carron Company; to Mr. A. Frost, Manager, Safety Products Ltd., and to Mr. M. Simpson for *Fig.* 164.

ACUTE RENAL FAILURE AFTER SURGICAL OPERATION AND HEAD INJURY

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ALTHOUGH many observations have been made in the last fifteen years upon acute renal failure (Bywaters, 1944; Maegraith, Havard, and Parsons, 1945; Lucke, 1946; Darmady, 1947; Strauss, 1948; Bull, Joekes, and Lowe, 1950; Oliver, MacDowell, and Tracy, 1951; Swan and Merrill, 1953; Brun, 1954) and its concomitant histological feature of acute tubular necrosis, the number of cases reported after head injury or after surgical operation is small. When such reports occur they are often included among those of larger numbers of cases of renal failure following events such as incompatible blood transfusion, poisoning, or abortion, so that details of the disease in surgical patients are submerged. The majority of cases of acute renal failure occurring in the Radcliffe Infirmary within the last six years have, however, followed surgical operation or head injury. In this account of them, emphasis is placed upon those aspects in which some differed clinically, biochemically, and histologically from other groups of patients in whom renal failure has been described.

PATIENTS

Acute renal failure was defined as occurring when the blood-urea rose above 100 mg./100 ml. and the urinary urea concentration fell below 2·0 g./100 ml. in patients without previous renal disease (Taylor, 1957). Of 42 patients who developed renal failure after operation or head injury, 37 (88 per cent) died and 5 (12 per cent) lived. Eleven of those who died showed at necropsy antecedent renal damage, not recognized in life, but of sufficient severity to be regarded as contributing significantly to post-operative renal failure. The distribution of cases among the major surgical subdivisions is shown in *Table I*. It will be noted that all those with head injury died and that a high proportion of the abdominal cases (47 per cent) had previously suffered significant renal damage. Several of the patients with head injury had also suffered injury to other parts of the body.

Further description in this paper is limited to the 31 patients who developed acute renal failure without evidence of previous renal disease, 26 of whom died (84 per cent). Renal failure was considered to be the prime cause of death in 9 of these patients and to be contributory in 6. In the remaining 11 patients death was considered inevitable, irrespective of acute renal failure, because of initial injury and/or complications, e.g., severe brain damage after head injury, or peritonitis following abdominal surgery. All patients were treated on high-calorie, low-protein diets with fluid intake restricted to balance external losses, as described more fully elsewhere (Taylor, 1957).

Table I.—THE CLASSIFICATION OF CASES OF RENAL FAILURE OCCURRING AFTER HEAD INJURY OR SURGICAL OPERATION

	Abdominal Surgical	*Neuro-surgical*	*Other Surgical*	*Head Injury*	*Total*
All Patients :					
Survived	2	1	2	0	5
Died, no previous renal disease	7	5	2	12	26
Died, with previous renal disease	8	0	0	3	11
Patients with Acute Renal Failure :					
Time of onset of renal failure					
Early—within 72 hours	5	2	3	6	16
Late	4	4	1	6	15
Hypotension					
None	1	2	1	3	7
At or immediately after injury or operation	3	2	2	4	11
Remote	5	2	0	5	12
Oliguria					
None	2	3	0	4	9
Following injury or operation	4	2	4	5	15
Terminal	3	1	0	3	7
Specific gravity of urine					
1·006–1·014	3	1	3	3	10
1·014–1·018	2	1	0	2	5
Above 1·018	1	3	0	4	8
Inadequate records	3	1	1	3	8
Plasma/urine chloride ratio					
2/1–4/1	1	0	3	1	5
Above 4/1	5	5	1	9	20
Inadequate records	3	1	0	2	6

CLINICAL FINDINGS

Onset of Acute Renal Failure.—In 16 patients (52 per cent) the onset of acute renal failure was early, occurring within seventy-two hours of injury or operation. Thirteen of these patients had associated hypotension. Twelve patients died. The prime causes of death were renal failure in 6 and cerebral damage in 4. Four of the five survivors thus came from this group.

The remaining fifteen patients experienced a late onset of acute renal failure, between the fourth and nineteenth days after operation or trauma, and usually in association with the development of severe complications such as pneumonia, peritonitis, or intestinal obstruction, in most cases with hypotension. Only one patient of this group survived.

Renal failure was considered to be the prime cause of death in only 3 patients, 2 of whom had suffered head injury, and a contributory cause in 5.

Hypotension.—Details of the pre- and post-operative, or post-traumatic, blood-pressure are available for 30 patients (*Table I*). In 7 the systolic blood-pressure was never recorded as falling below 100 mm. Hg. In all but one of these patients, however, there are gaps of up to four hours in the records so that the possibility of such a fall exists, although there was never other clinical evidence to suggest its occurrence.

Systolic pressures below 100 mm. Hg were observed at the time of, or within twenty-four hours of, operation or injury in 11 patients, and at a later period in 12. Among the latter group there were 3 patients in whom the onset of renal failure preceded the onset of hypotension. Ten of 31 patients (32 per cent) thus developed acute renal failure without preceding evidence of hypotension and in only 2 of them was there evidence of considerable blood-loss. The proportion whose systolic blood-pressure never fell below 80 mm. Hg was larger still (57 per cent). In several of the patients who did develop hypotension its duration was slight; in 2 it was less than 2 hours and in another 4 less than 9 hours.

Both early and late onsets were seen in patients without hypotension, but where hypotension occurred early, renal failure began early, and where hypotension occurred with the onset of complications, renal failure was correspondingly late.

Urinary Output (*Table I*).—Nine patients, one of whom survived, excreted more than 300 ml. of urine daily throughout the period of acute renal failure, and following Bull, Joekes, and Lowe (1950) were considered not to be oliguric. The maximum daily volumes of urine excreted by these patients during the period when the blood-urea and serum potassium concentrations were rising and the plasma bicarbonate falling, varied from 800 ml. to 1960 ml. and the minimum daily volumes from 350 ml. to 510 ml. Of the 22 patients who developed oliguria, 15 (4 of whom survived) did so within 48 hours of trauma or operation. Seven patients, all of whom died, became oliguric terminally, usually in association with the onset of complications. In 3 of these patients, acute renal failure preceded the onset of oliguria, so that in 12 patients altogether, oliguria would have proved an unreliable diagnostic guide. Of the 16 patients with early onset of acute renal failure, 13 had developed oliguria within 48 hours and 3 were never oliguric. Of the 15 patients with a late onset, 6 were never oliguric and 7 became oliguric terminally.

BIOCHEMICAL FINDINGS

Urinary Specific Gravity (*Table I*).—The urinary specific gravity in 10 patients was fixed from the onset within the range 1·006–1·014. In 5, maximal values within the range 1·014–1·018 were recorded between the second and eighth days; and in 8, values above 1·018. Thus in approximately one-third of the patients in whom records are available the urine was of unexpectedly high specific gravity, despite its low urea concentration.

Plasma/Urine Chloride Ratio (*Table I*).—The plasma chloride concentration, in all but 4 cases, was normal (90–106 mEq./l.) or low, and the urinary chloride concentration generally low (less than 30 mEq./l.). The ratio of plasma and urinary chloride concentrations was thus 4 : 1 or less in only 5 patients and exceeded this value in 20, in 7 instances reaching infinity. Only a small proportion of patients therefore showed uncontrolled loss of chloride in the urine (Bull, Joekes, and Lowe, 1950), indicating that tubular function was preserved with respect to chloride ion in the majority of cases. In 11 of the 20 patients with high plasma/urine chloride ratios, data are available over a period of at least 4 days, but in 9 it is possible that the patient may have died before tubular damage became sufficient for uncontrolled urinary loss of chloride to occur.

Blood-urea, Serum Potassium, and Plasma Bicarbonate Concentrations.—In association with the rise in blood-urea there was the tendency, usual in renal failure, towards abnormally high serum potassium levels and low plasma bicarbonate concentrations, but there was a relatively large number of patients (13) in whom the serum potassium concentration remained within normal limits (3·6–5·4 mEq./l.). Included among these 13 are 4 of the patients who survived, in 3 of whom recovery occurred within 4 days, so that the serum potassium concentration, although rising, never exceeded the normal range. In 4 patients who died within 3 days, the serum potassium similarly never reached abnormally high levels. In 4 patients oliguria did not occur and it is possible that normal serum potassium concentrations were maintained by continuing urinary excretion of this ion.

The fall of plasma bicarbonate concentration was related to the urinary output. Thus all 3 patients with a normal plasma bicarbonate (20–30 mEq./l.) were without oliguria. In 15 oliguric patients the mean minimum plasma bicarbonate concentration was 12·5 mEq./l., whereas in 8 non-oliguric cases it was significantly higher at 18·5 mEq./l. It would seem therefore that with a urine flow of 300 ml./day or more, the renal tubules may still retain some ability to control acid-base balance.

It will be noted that a considerably greater proportion of patients had low plasma bicarbonate concentrations than had raised serum potassium levels. The records show further that in 14 patients the fall of plasma bicarbonate concentration below normal preceded the rise of serum potassium concentrations to abnormal levels.

HISTOLOGICAL FINDINGS

Post-mortem examination was possible in 24 of the 26 patients who died. In 15 of them the kidneys showed the characteristic features of acute tubular necrosis, with pigmented casts, foci of tubule destruction, and interstitial inflammatory cell infiltration. In the remaining 9 cases none of these changes occurred. The kidneys appeared entirely normal in 1, while the other 8 all showed in varying degrees some of the appearances emphasized by Brun (1954): flattening of the epithelium of proximal and distal convoluted tubules, dilatation of the distal tubules, and marked hydropic change in some of the proximal convoluted tubules. Interstitial œdema and inflammatory cell infiltration were not, however, a feature of these cases. The same changes

were also found in cases with acute tubular necrosis of short duration, and are interpreted as being pre-necrotic. In both groups of patients crystals of the sort usually described as leucine were present in tubules; they were most numerous in those with coincident liver damage.

Of those patients with an early onset of acute renal failure, 10 showed acute tubular necrosis and

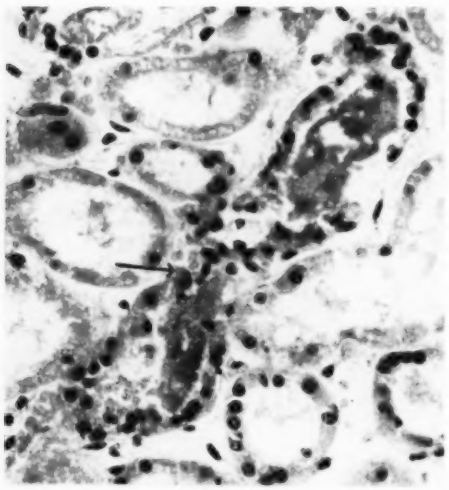

FIG. 170.—A necrotic tubule is shown containing a pigmented cast. The arrow points to a breach in the wall where a hæmorrhage from a peritubular capillary enters the lumen and is continuous with the cast. Three days' anuria. Hæmatoxylin and eosin. (× 300.)

2 did not. Of those with a remote onset 5 showed acute tubular necrosis but 7 did not.

In 3 cases with early necrotic changes and of short clinical duration (2–4 days), small hæmorrhages were found from capillaries into distal convoluted tubules through a necrotic part of the tubular wall. These appeared to be giving rise to casts (*Fig.* 170) indistinguishable in form and staining properties from the ordinary pigmented casts. This process may perhaps be of significance for the genesis of pigmented casts in patients with acute renal failure in whom intravascular hæmolysis and muscle damage have not occurred. It is of interest that Kark, Muehrcke, Pirani, and Pollak (1955) have described capillary hæmorrhages into damaged tubules in sub-acute glomerulonephritis and suggest that this may be the origin of the hæmaturia rather than glomerular leakage.

Correlation of Clinical with Histological Findings.—In *Table II* the clinical and biochemical findings of cases with and without acute renal tubular necrosis are compared. No differences between the two groups could be detected with respect to the presence or absence of hypotension, but there was otherwise a general tendency for patients without tubular necrosis to show less severe changes than those with. Thus oliguria and isosthenuria were less common among the former. Changes of blood-urea, serum potassium, and plasma bicarbonate concentration were also less marked in the non-necrotic group, probably as a result of two factors. First, 5 of the non-necrotic group died within the first five days, whereas 10 of the necrotic group survived for longer periods and consequently developed more severe biochemical abnormalities. Secondly, relatively few of the patients without tubular necrosis were oliguric and could consequently excrete urea and potassium more readily than those with oliguria. There is thus no satisfactory clinical or biochemical evidence of two distinct groups of patients corresponding to the two different histological groups, although it is possible that statistically significant differences of urine flow and urinary specific gravity could be established if a larger series of patients was studied. The clinical and biochemical findings are thus in accord with the view of Mallory (1947), that histological changes such as those in the non-necrotic kidneys represent

Table II.—CLINICAL AND BIOCHEMICAL FINDINGS IN CASES OF ACUTE RENAL FAILURE

	Acute Tubular Necrosis	*Without Tubular Necrosis*
Hypotension		
None	2	1
At trauma or operation	5	4
Remote	7	4
No records	1	0
Oliguria		
None	2	5
Terminal	5	2
Throughout	8	2
Specific gravity		
1·008–1·014	3	1
1·014–1·018	3	1
Above 1·018	3	5
No records	6	2
Plasma/urine chloride		
2–4	3	0
Above 4	9	7
No records	3	2
Blood-urea mg./100 ml.		
100–200	4	2
200–400	4	7
Above 400	7	0
Serum potassium		
Below 5·4 m.Eq./l.	4	5
Above 5·4 m.Eq./l.	9	4
No records	2	0
Plasma bicarbonate		
Above 20 m.Eq./l.	0	2
Below 20 m.Eq./l.	12	3
No records	3	4

a phase of an essentially continuous process ending in fully-developed acute tubular necrosis. Our finding such changes in cases with early renal tubular necrosis also supports this view.

DISCUSSION

Early and Late Renal Failure.—From the clinical evidence which has been presented it is possible to differentiate early and late types of acute renal failure. The early type begins within seventy-two hours of trauma or operation and generally in direct association with the events occurring at that time. In the late type, occurring after seventy-two hours, acute renal failure arises secondarily to the onset of complications. The different features in the two groups are contrasted in *Table III*. In the early group there is a relatively higher survival rate, death occurs principally from renal failure or initial injury, there is a high incidence of early hypotension and oliguria, and at post-mortem the characteristic features of acute tubular necrosis are usually seen. In the late group, death from complications is the usual termination, there

is either no oliguria, or else oliguria and hypotension arise in association with the onset of complications, and at post-mortem only about half the cases exhibit acute renal tubular necrosis.

Although a clinical division of cases into groups with early and late onset may thus be made, it does not seem likely from the arguments already advanced that fundamentally different pathological processes are at work in the kidneys of the two groups.

Table III.—THE CLINICAL AND PATHOLOGICAL FEATURES OF EARLY AND LATE ACUTE RENAL FAILURE

	Acute Renal Failure Early Onset per cent	*Acute Renal Failure Late Onset* per cent
Survived	25	7
Cause of death		
Initial injury	33	0
Renal failure	50	20
Complications	17	80
Hypotension		
None	20	27
Within 24 hr.	67	6
Late	13	67
Oliguria		
None	19	40
Within 48 hr.	81	13
Late	—	47
Acute tubular necrosis		
With	83	42
Without	17	58

Renal Function.—The clinical course of acute renal failure among patients without accidental or operative trauma (Bull, Joekes, and Lowe, 1950) may be divided into four phases—onset, oliguria, early diuresis, and late diuresis—each defined in terms of renal function. Only 3 patients in the present series progressed to recovery through these stages, about half dying while oliguric. The clinical course of the remaining cases differed from the above pattern, 9 patients were never oliguric, and 3 passed from a non-oliguric renal failure into terminal oliguria or anuria, thus reversing the usual course of renal failure when associated with mismatched blood transfusion or abortion.

The urinary specific gravity and plasma/urine chloride ratio during renal failure after head injury or operation showed differences from previously described findings in acute renal failure associated with other conditions. During the oliguric and early diuretic phases, Lucke (1946) and Bull and Dible (1953) have found the urinary specific gravity to be usually about 1·010, and in 8 of 10 cases of non-traumatic acute renal failure occurring in the Radcliffe Infirmary within the last three years the urinary specific gravity ranged from 1·004 to 1·014. After head injury or operation, however, 6 of 23 patients had a specific gravity greater than 1·020 on the second to eighth days and 12 patients had values greater than 1·015. These observations are more in accord with those of Darmady (1947), who found in battle casualties that the specific gravity of the urine remained between 1·014 and 1·018. Burnett, Shapiro, Simeone, Beecher, Mallory, and Sullivan (1947) found, however, in battle casualties that though the mean urinary specific gravity on the second to fourth days was 1·015, it fell on the fifth to seventh days to 1·012. The difference between plasma/urine chloride ratios is even more striking. Bull, Joekes, and Lowe (1950) found that in the oliguric and early diuretic phases all their patients had plasma/urine chloride ratios of approximately 2 to 1, and a similar ratio was observed in 6 of 10 non-traumatic cases occurring in the Radcliffe Infirmary. Only in 5 patients of the present series, however, was the ratio 4 to 1 or less. It would seem that with respect to concentrating the urine and conserving plasma chloride, tubular function is less drastically disturbed in some patients in whom renal failure has followed head injury or operation than in those in whom it has followed mismatched transfusion or abortion. It is known that the normal metabolic response to trauma and operation results in diminished excretion of water and of sodium and chloride. It may be wondered whether the factors mediating such a response continue to operate on the kidney even when acute renal failure supervenes, and whether they are responsible for the high specific gravities and high plasma/urine chloride ratio that have been seen in the present series.

Mechanism of Oliguria.—The mechanism of oliguria in acute renal failure remains unsolved. Obstruction of the tubular lumen by casts was at one time thought to be the principal factor in diminishing urine flow (Baker and Dodds, 1925), but other possible explanations have been advanced, such as disruption of tubular lumen (Oliver, MacDowell, and Tracy, 1951), diminished glomerular filtration as a result of hypotension with glomerulo-tubular imbalance (Bywaters and Dible, 1942), shunting of blood-supply from renal cortex to medulla (Trueta, Barclay, Daniel, Franklin, and Prichard, 1947), and increased intrarenal pressure (Peters, 1945). Many or all of these mechanisms may possibly be operating in differing degrees and at different times in any one patient, so that no complete analysis of the role of each factor is possible. Attention may, however, be drawn to the fact that only 2 of 15 patients with acute renal tubular necrosis failed to become oliguric, whereas of those without tubular necrosis, 5 of 9 failed to do so. Since the presence of casts is a feature distinguishing kidneys with acute tubular necrosis from those without, these findings would be compatible with the view that physical obstruction of tubules by casts might contribute to the diminution of urine flow in those patients in whom the daily urinary output falls below 300 ml./day.

Comparison with Acute Renal Failure following Non-traumatic Events.—The observations recorded above indicate that after head injury or operation the clinical and biochemical features of acute renal failure vary widely. On the one hand may be seen the frequently-described picture of a hypotensive episode with subsequent oliguria, failure of tubular function, and post-mortem tubular necrosis, whereas at the other extreme, acute renal failure may occur without hypotension or oliguria, with evidence of tubular ability to retain chloride, and yet with equally obvious tubular damage at necropsy.

The clinical picture of acute renal failure is therefore much less clear-cut than after mismatched transfusion, abortion, or simple hæmorrhage. Thus there was no oliguria in about one-third of the cases, and the late onset of renal failure in association with complications is peculiar to post-operative or post-traumatic cases. The mortality in this series of patients was high (84 per cent) compared with that

of 40 per cent in a series of 10 non-traumatic cases treated similarly in this hospital, and with that of 36 per cent found by Bull, Joekes, and Lowe (1949). Teschan, Post, Smith, and others (1955) found a similarly high mortality (80 per cent for post-traumatic renal failure in Korean battle casualties). Differences of urinary specific gravity and plasma/urine chloride ratio between post-traumatic and non-traumatic acute renal failure are also noted. Lastly, it may be mentioned that despite high caloric, non-protein diets our patients experienced a large mean daily rise of blood-urea concentration of 51 mg./100 ml., whereas in the non-traumatic cases the rise was less, 30 mg./100 ml./day (Taylor, 1957). Bull, Joekes, and Lowe (1950) found an even smaller increase of 8–26 mg./100 ml./day.

These differences between acute renal failure occurring after trauma and after non-traumatic events may represent little more than the superimposition of the clinical and metabolic effects of trauma upon the same fundamental pathological processes in the kidney. They do, however, pose certain diagnostic and therapeutic difficulties which have been discussed elsewhere (Taylor).

SUMMARY

1. Acute renal failure, defined as the occurrence of a blood-urea concentration above 100 mg./100 ml. with a urinary urea concentration below 2·0 g./100 ml. in patients without previous renal disease, has been described after civilian head injury or surgical operation in 31 patients, of whom only 5 survived.

2. Acute renal failure in such patients may occur immediately after injury or operation, or may arise, usually in association with complications, after several days of apparently normal renal function.

3. One-third of the patients developed acute renal failure in the absence of evidence of hypotension and about one-third always secreted more than 300 ml./day of urine during the period when the blood-urea concentration was rising and the urinary urea concentration was low.

4. Renal tubular function was, in several patients, partially preserved, as indicated by high plasma/urine chloride ratios, relatively high urinary specific gravities and, in non-oliguric patients, only slightly subnormal plasma bicarbonate concentrations.

5. Acute renal tubular necrosis was found at autopsy in 15 of 24 cases. Eight cases showed histological changes which are interpreted as pre-necrotic.

6. Evidence is presented that the characteristic pigmented casts of acute tubular necrosis may arise from capillary hæmorrhages into tubules.

7. Differences between acute renal failure after head injury or operation and acute renal failure following non-traumatic events are emphasized. It is suggested that such differences may result from superimposing upon damaged kidneys the increased protein catabolism and diminished excretion of water and chloride which normally follow trauma.

We wish to thank the surgeons of the Radcliffe Infirmary for access to patients under their care; Mr. J. R. P. O'Brien and the staff of the Department of Clinical Biochemistry, by whom many of the estimations were made; Mr. I. T. Hinton for preparation of the photomicrograph; and Dr. A. H. T. Robb-Smith for encouragement and for advice over histological interpretation.

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TWO AND A HALF YEARS' SURVIVAL OF A GRAFTED ABDOMINAL AORTIC ANEURYSM WITH HISTOLOGICAL STUDIES

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One of our male patients with an abdominal aortic aneurysm treated by excision, endarterectomy, and insertion of a freeze-dried homograft died two and a half years later from coronary thrombosis. We have been unable to find any reference in the literature to a patient surviving more than one year after the insertion of a similar graft.

Fig. 171.—The post-mortem specimen showing the satisfactory result 2½ years after the replacement of the distal portion and bifurcation of the aorta by a homograft. (× ¼.)

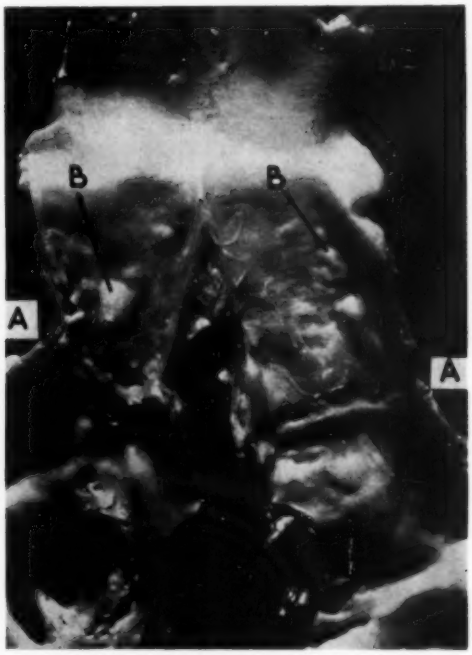

Fig. 172.—Distal portion of graft showing the lines of anastomosis in the common iliac arteries (A). The plaques of atheroma (B) which are present in the graft are not so severe as those in the patient's arteries. (× ¼.)

At operation, failure to wash out any soft clot before the end of the grafting procedure delayed restoration of the peripheral pulses, but probably had no permanent ill effects. During the period of survival we were able to watch the change in the patient's peripheral pulses as he developed intermittent claudication; finally we have detailed histological studies of his vessels and of the graft.

Areas of atheroma were present in the graft when it was taken from a man aged 39, and apparently these areas were not affected by the freeze-drying process which was used to preserve the graft.

Externally at autopsy the graft appeared like a new vessel, and the area of the aorta which had been endarterectomized looked very much healthier than the rest of the patient's aorta. Histological investigations showed that in the graft a continuous new inner layer had been formed by a monolayer of viable cells, and growth of fibrous tissue into the outer half of the media had occurred along its entire length. The graft was thus more completely assimilated than any reported hitherto.

Incidentally, sections show the presence of french chalk from the surgeon's gloves in the outer layers of the graft; whilst this has helped in defining layers, yet it shows, in its persistence, the possible danger to talc granuloma.

CASE REPORT

H. J., born 1893, a fitter's mate at a power station, noticed a swelling in his lower abdomen in 1952, and 18 months later felt pain in the middle of his back

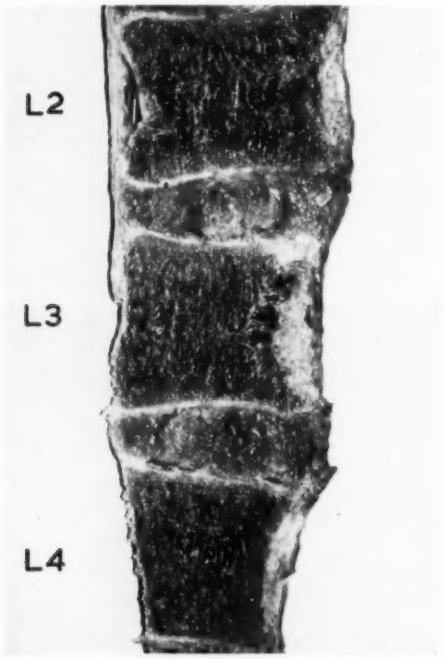

FIG. 173.—Erosion of the third lumbar vertebra by the aortic aneurysm. (× ⅓.)

radiating at first to the left and after a few months to the right pubic tubercle, but never to both sides at the same time; he had also pain in the buttocks over a short period. The pains were relieved by analgesics but not by change of posture.

Clinical examination showed a man of 61 years with an aneurysm of the lower part of his abdominal aorta. All the major pulses were present in the lower limbs. His blood-pressure was 240/110. The urine, of low specific gravity, did not contain albumin and the intravenous pyelogram showed good excretion with normal outlines. The E.C.G. indicated left ventricular preponderance with no evidence of a recent myocardial infarct.

Laparotomy revealed an aneurysm involving the abdominal aorta and dilatation of the proximal parts of the common iliac arteries, but the wall of the aorta below the renal arteries seemed to be too thickened to allow resection and grafting; a Colt's umbrella was inserted into the aneurysm. Convalescence was satisfactory but the pain in his back persisted and became worse.

About this time, one of us (H. S. S.) saw Professor Rob operating for Leriche's syndrome, and appreciated that although the aorta below the renal arteries might be severely arteriosclerotic it could be endarterectomized and made suitable for suture to a graft.

A second operation was accepted by the patient and was carried out after the laparotomy. The anæsthetist (Dr. A. T. Hawthorn) used hibernation, as it was anticipated that the aortic clamp might have to be put on proximally to the renal vessels.

AT OPERATION.—The aneurysm was isolated through a midline incision by a direct retroperitoneal approach; the tortuous common iliac arteries and the patent inferior mesenteric artery were divided; in the area just below the renal arteries the aorta was a little dilated but allowed fairly easy dissection for application of a Blalock clamp. The aneurysm was then removed, some of its wall being left on the inferior vena cava, and any bleeding lumbar arteries were sutured. The divided upper end of the aorta showed severe calcification and ulcerated atheroma. This pultaceous tissue was scraped out, but even so, a cutting needle with No. 3·0 silk had to be used for the suture of the aorta to the graft. After this proximal anastomosis had been done, the end-to-end anastomosis of the graft to the divided common iliac arteries was completed before the clamp on the aorta was released.

Source of Graft.—The donor was a man aged 39 years who had been killed in a road accident. The graft was taken under aseptic conditions, sterilized by immersion in 1 per cent ethylene oxide at 4° C. for one hour,

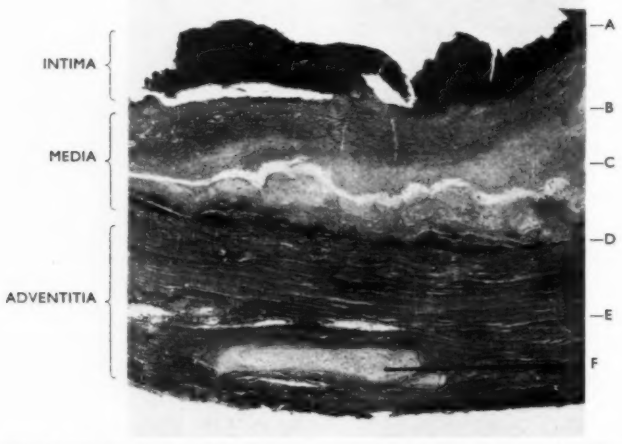

FIG. 174.—Section of patient's aorta taken from immediately above the graft. A, Fibrinous layer; B, Collagenous fibres; C, Atheromatous plaque; D, Elastic fibres; E, Adventitia; F, Nerve ganglion. Elastic van Gieson. (× 30.)

snap-frozen at −79° C., and freeze-dried by the method described by Flewett, Zinnemann, Oldfield, Shucksmith, and Dexter (1955). It was reconstituted in normal saline containing 100 units per ml. penicillin, 100 μg. per ml. streptomycin, and 50 units per ml. heparin. Atheroma was found in parts of the graft not used.

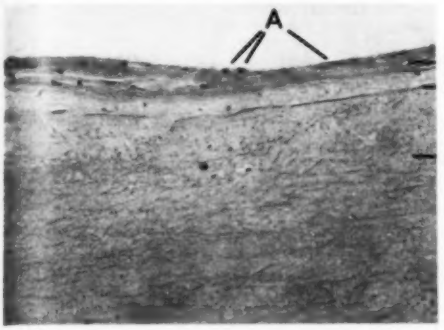

FIG. 175.—Section taken from central portion of aortic graft, showing inner layer. A, Nuclei of flattened cells lining the lumen of the aorta; B, Fibrous tissue; C, Internal elastic lamina; D, Media. H. and E. (× 78.)

Clinical Progress.—By the time the patient was returned to the ward, both common femoral and the left popliteal pulses were of good amplitude, but the right popliteal and posterior tibial pulses could not be felt. Twelve hours later all major pulses were palpable except the right posterior tibial; indeed, a month elapsed before this pulse was palpable. Immediately after the operation the pain in the patient's back disappeared and his convalescence was satisfactory.

Five months after the operation he returned to a relatively hard job which entailed a two- to three-mile walk from his home and he continued to work for some time although he had attacks of dizziness with vomiting. Intermittent claudication developed in the left calf muscle nine months after the operation; at that time all the major pulses at the ankle were present though they were diminished after exercise. Although this symptom persisted and his walking distance was reduced to 300 yards, it was a year before the left popliteal and posterior tibial pulses disappeared; even then the major pulses were still palpable in the right lower limb. This was the picture of his peripheral pulses two years after resection of the aneurysm and six months before his death from coronary thrombosis.

POST-MORTEM FINDINGS.—All organs were examined and the relevant findings were as follows.

Heart.—Weight 600 g. The left ventricular wall was greatly hypertrophied. There was a yellow area of infarction, measuring approximately 5 cm. in greatest dimension, in the posterior wall of the left ventricle. The circumflex branch of the left coronary and the right coronary arteries were occluded by old thrombus and calcified atheroma. In the descending branch of the left coronary artery there was a severe degree of atheromatous change in the wall, with marked reduction in the lumen of the artery.

Aorta (*Fig.* 171).—The abdominal portion of the aorta had been excised, and replaced by a homograft 8 cm. long. Its proximal end was 5 cm. distal to the origins of the renal arteries, and it included the bifurcation of the aorta, 2·5 cm. of the right, and 3 cm. of the left common iliac artery. Dense fibrous tissue which surrounded the graft was particularly adherent to the anterior surface of the bodies of the lumbar vertebræ. The body of the third lumbar vertebra was eroded (*Fig.* 173).

The circumference of the patient's aorta immediately above the graft was 6·2 cm. At its narrowest point the circumference of the graft was 3·7 cm., and at its widest point, 4·3 cm.

All three lines of anastomosis were well healed and were marked by a line of white fibrous tissue. In places the black suture material was visible through a thin layer of translucent fibrous tissue. The endothelial surface of the graft was smooth, the only naked-eye abnormalities being an ulcerated area of atheroma 1·4 × 0·6 cm. on the posterior wall, 1 cm. from the upper end of the graft, and several small plaques of atheroma in the common iliac portions of the graft (*Fig.* 172). This appearance was in striking contrast to the patient's own vessels, the descending aorta, common iliac, external iliac, and femoral arteries showing severe atheromatous ulceration, calcification, and mural thrombi. The intimal surface of the portion of the patient's aorta, which had

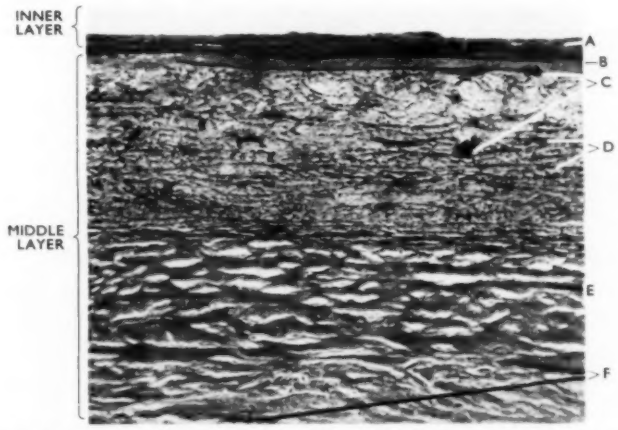

FIG. 176.—Section from aortic graft showing fragmentation of elastic fibres. A, Fibrous tissue; B, Internal elastic lamina; C, Calcium deposits; D, Fragmentation of elastic fibres; E, Dense collagenous bundles; F, Fragmented elastic fibres in outer half of media. Elastic van Gieson. (× 90.)

been subjected to thrombo-endarterectomy, appeared to be somewhat smoother than the rest of the patient's aorta, there was still severe atheromatous degeneration with ulceration.

The right femoral and left popliteal arteries were completely occluded and calcified.

Kidneys.—Although the main renal arteries were almost free from atheroma, there was considerable arteriosclerotic scarring of each renal cortex. All other organs appeared macroscopically normal.

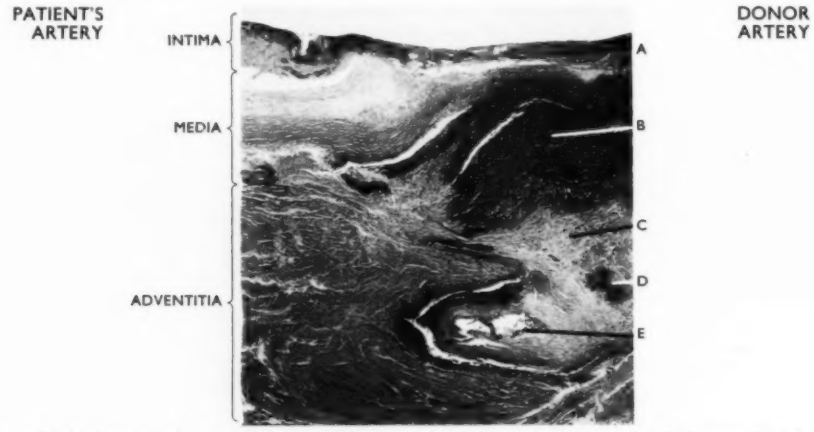

FIG. 177.—Proximal anastomosis of aortic graft. A, Fibrinous layer; B, Dense elastic fibres of grafted artery; C, Collagenous fibres; D, Collection of lymphocytes; E, Suture material. Elastic van Gieson. (× 30.)

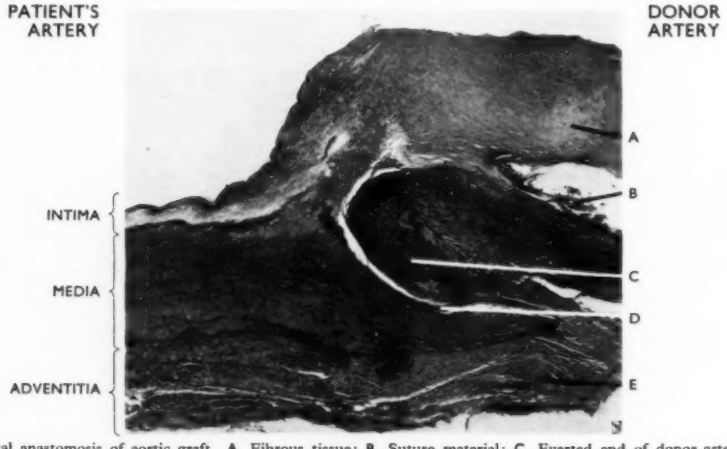

FIG. 178.—Distal anastomosis of aortic graft. A, Fibrous tissue; B, Suture material; C, Everted end of donor artery; D, Patient's internal elastic lamina; E, Collagenous fibres. Elastic van Gieson. (× 30.)

HISTOLOGY.—

Patient's Aorta (*Fig.* 174).—The architecture of the aorta was greatly distorted by severe atheroma (*Fig.* 174 C) involving the inner half of the vessel wall. No normal intima could be recognized and a thick layer of fibrin (*Fig.* 174 A) lined the aorta. The media, in relation to the patches of atheroma, consisted mainly of collagenous fibres (*Fig.* 174 B) with only irregular preservation of elastica (*Fig.* 174 D). The adventitia (*Fig.* 174 E) was formed by a dense layer of collagen, in which there was patchy lymphocytic infiltration.

Aortic Graft.—In the graft the anatomical layers were not defined in the same clear way as is seen in the normal aorta.

Inner layer: The intima varied in thickness from approximately 100 .. near the anastomosis to approximately 15 .. in the centre of the graft. It consisted of fibrous tissue throughout the length of the graft (*Fig.* 175 B) and the surface was lined by a single layer of flattened cells (*Fig.* 175 A). A thin layer of fibrin also covered the intima over a length of 1 cm. beginning 2 cm. below the proximal anastomosis.

Middle layer: For the greater part of the length the media appeared to consist of two layers, an inner one of dense devitalized elastic fibres (*Fig.* 177 B) and an outer layer of bundles of collagenous fibres (*Fig.* 177 C). In the inner half the elastic fibres appeared mainly to be intact and to stain normally, but in one area, at approximately 2 cm. from the distal end of the graft, the elastica was fragmented (*Fig.* 176 D). There were also small deposits of calcium (*Fig.* 176 C) in this layer, and in a section taken from the bifurcation, severe fatty infiltration

of the intima and of the inner half of the elastica could be seen (*Fig.* 179). Only isolated fibroblasts could be identified in the elastica, but the collagenous outer layer of the media had apparently been formed by replacement of the elastica by fibrous tissue of the host (*Fig.* 176 E). Fragmented remains of elastica (*Fig.* 176 F) could be identified between the dense bundles of collagen.

Outer layer: The adventitia consisted mainly of dense collagenous fibres in which were present arterioles, nerves, and collections of lymphocytes. The line of junction between the collagenous layer of the media and

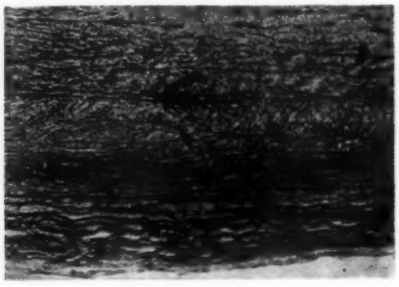

FIG. 179.—Section taken from aortic graft showing the presence of fat (stained red) in the intima and inner part of media. (× 66.) Scharlach R and hæmatoxylin.

the periarterial fibrous tissue could be readily identified by a row of foreign-body giant cells. These had formed around doubly refractile crystalline particles, which were most probably from the french chalk on the surgeon's gloves.

LINES OF ANASTOMOSIS.—

Proximal Anastomosis (*Fig.* 177).—The two ends of the arteries appeared to be firmly joined by dense fibrous tissue. The layer of fibrin (*Fig.* 177 A) which lined the wall of the patient's aorta extended across the site of the anastomosis and over the intima of the graft for about 3 mm.

An aggregate of foreign-body giant cells was present around suture material (*Fig.* 177 E) and scanty lymphocytes (*Fig.* 177 D) were seen in the adjacent fibrous tissue.

Distal Anastomosis (*Fig.* 178).—The end of the donor artery had been slightly everted (*Fig.* 178 C), causing it to appear rounded. This had been sutured to the inner aspect of the internal elastic lamina (*Fig.* 178 D) of the host's common iliac artery. However, fibrous tissue from the patient's intima had formed a thick layer over the end of the graft (*Fig.* 178 A). The two types of suture material which had been used during the operation were identified in the wall of the graft.

DISCUSSION

Clinical.—The presenting symptom of the abdominal aortic aneurysm in this case was pain in the first lumbar distribution, at first on the left and then on the right, together with pain in the lumbar region of the back. Autopsy showed that it was the third lumbar vertebra which was eroded. It is difficult to see how erosion of the front of a vertebral body gives pain in a root distribution, and particularly too when the pain is at the level of L.1, and the vertebra maximally involved is L.3. Equally, an explanation for the disappearance of the pain immediately after excision of the aneurysm is difficult.

The immediate post-operative convalescence was uncomplicated; there was no paralytic ileus and the case is an example of the impunity with which the inferior mesenteric artery can be divided.

At the time of the operation we did not attempt to ensure that any soft clot developing near the clamps was washed out by a free flow of blood before completing, say, the left iliac anastomosis, allowing this side to flow while the right-side anastomosis was completed. The omission presumably accounts for the return of the left tibial pulse twenty-four to thirty hours later, and the right posterior tibial pulse some weeks later, but we record these facts to show that, even so, full pulses did eventually return.

The problem of intermittent claudication in the calves, when the major peripheral pulses are present, is always intriguing. Usually the peripheral pulse disappears on exercise, but this is not always so; in this patient, the pulse did diminish with exercise, but had not disappeared even a year after the intermittent claudication had presented. However, after a further year there was clinical evidence of major vessel blockage. The possibility of disease of small muscle arteries being the early cause of the claudication was kept in mind, and at autopsy muscle tissue was removed for study; this showed the vessel in the muscle to be normal.

Histological.—Creech, De Bakey, Self, and Halpert (1954) have well summarized the histological findings by stating that after about one year "the homograft appears grossly and microscopically as a new vessel formed about an elastic tissue framework with a thickened intima, a compressed media, and broad adventitia".

Shumacker, Kajikuri, Grice, Rodriguez, Riberi, Moore, and Siderys (1957) have classified results as "good" when the graft is widely patent, with a smooth lining, minimal deposition of fibrin, and minimal degrees of calcification and atheromatous changes. The graft under consideration fulfils all these criteria.

The histological changes in grafts which have been inserted up to 360 days have been described fully by De Bakey, Creech, Cooley, and Halpert (1954). The present case is complementary to the ten which these authors have described, in that survival has lasted for 2½ years after operation.

Inner Layer.—In De Bakey and others' cases the inner surface of the central portion of the graft was formed by elastic fibres of the media itself. Our findings differed in the fact that the whole length of the graft was lined by a layer of fibrous tissue covered by a single layer of cells. This point is also mentioned by Sauvage and Wesolowski (1955), who state that the extent of the lateral spread of fibrous tissue from the anastomosis along the inner surface of the graft rarely reaches the centre of grafts which are 6 cm. in length. This difference in findings may be due to the fact that all these cases were investigated for periods of less than one year. One can deduce from various figures published that fibrous tissue grows along the inner surface of a graft from either end at the rate of approximately 3 cm. per year. In the present case the whole length had been covered. Thus it appears that the ingrowth into the graft of the recipient's tissue elements is not a process limited in space or time, but will extend,

if survival of the recipient is sufficiently long, to the whole length of the graft.

Media and Adventitia.—It is generally accepted that in homografts the inner elastic fibres condense and become impervious to the ingrowth of fibrous tissue from the periarterial host tissues. In this graft, in the inner half of the media, the elastic fibres are largely intact, although in the outer half they have become fragmented and replaced by dense collagenous fibres. The wall appears to have been strong enough to take the strain of the blood-pressure, as there is no evidence of dilatation. Most authors suggest that the integrity of the inner condensed layer of elastica prevents dilatation of the graft during the first six months until the host's collagenous fibres are thick enough to take the strain. Rosenberg, Henderson, Douglas, Lord, and Gaughran (1957) disagree with this view, and suggest that the elastica is relatively weak and that the collagen which develops outside the elastic structure may be the important factor. However, it is to be noted in heterografts, in which there is a tendency for the elastica to disintegrate, that dilatation and aneurysmal formation usually occur (Creech and others, 1954; Wesolowski and Sauvage, 1953). Sauvage and Wesolowski (1955) suggest that freeze-drying delays, but does not prevent, the loss of continuity of elastic tissue in heterografts.

Degenerative Changes.—Sauvage and Wesolowski (1955) state that calcification is least in fresh grafts, maximal in grafts dried by evaporation, and intermediate in frozen and freeze-dried grafts. Creech and others state that calcium deposits have been observed in the media of experimental homografts one to two years old, although no retrogressive changes were noted in a human homograft one year after transplantation. The calcium deposition in the present case was slight. Sutherland, Williamson, Zinnemann, and Shucksmith (1958) have found persisting deposition of fat in the intima and inner part of the media of stored arteries after the process of freeze-drying. The distribution of fat was similar in the present case, and it seems highly probable that it was present before transplantation. The time of deposition of the calcium cannot be determined, but this also may have been present in the stored specimen.

Sutherland and others have found no histological evidence of disruption of freeze-dried preparations by lipoid deposits. In this they differ from the statement by Eastcott, Holt, Peacock, and Rob (1954) who doubt the suitability of freeze-dried grafts from donors with lipoid deposits in the intima and media. On the other hand, Szilagyi, Overhulse, Shonnard, and LoGrippo (1954) state that on occasions they have used freeze-dried grafts from donors in the fifth decade of life, with satisfactory results.

It appears from the case described here that with the technique used by Flewett and others (1955) vessels with soft atheromatous changes can be used successfully, thus enabling more material to become available for artery banks.

SUMMARY

1. A male, aged 61 years, with an advanced aneurysm of the abdominal bifurcation survived for 2½ years after the grafting of a sterilized and freeze-dried vessel from a donor aged 39. Endarterectomy of the upper abdominal aorta had to be done.

2. During this period the patient developed intermittent claudication in the left leg, with the major ankle pulses still persisting for a considerable time.

3. At autopsy the graft looked like a new vessel and the endarterectomized part of the recipient's aorta looked better than the rest.

4. Histologically, the graft had a new and viable lining of the inner layer along the whole length of the graft. The middle layer consisted of an inner half of devitalized elastic fibres and an outer half of infiltrating collagen along the whole length. Small deposits of calcium and pre-existing fatty infiltration in the intima and inner part of the media were also present. In the newly-formed outer layer, french chalk from the surgeon's gloves could be identified.

5. Ingrowth of the recipient's tissue elements extended over the whole length of the graft.

6. Presumably pre-existing soft atheromatous plaques in the graft did not impair its function or strength during 2½ years.

Addendum.—Since this paper was submitted for publication, several articles have been published relating to the survival of patients for periods up to four years following the replacement of abdominal aortic aneurysms by homografts.

An excellent histological study has been published by Szilagyi, McDonald, Smith, and Whitcomb (1957), describing the changes which occur in aortic homografts at various time intervals up to 23 months. On the whole, their findings agree with our results.

Acknowledgements.—We are indebted to the Board of Governers of the United Leeds Hospitals for generous financial aid and grant for the Leeds Tissue Bank; we should like to thank Professor C. L. Oakley and Dr. Wm. Goldie for advice and constructive criticism, Dr. D. G. F. Harriman for investigating calf muscle, and Mr. J. Hainsworth for the photographs.

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TUMOURS OF THE BREAST

A STUDY EMPLOYING A HISTOCHEMICAL TECHNIQUE

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EMPHASIS is placed to-day on the early diagnosis of malignant tumours. This applies, with special significance, to tumours of the breast, since they are the commonest growths encountered by the surgeon.

Mistakes in diagnosis are made, but although an occasional malignant tumour, whether in its earliest stages or in some atypical form, may be overlooked until its continued growth or the occurrence of metastases compels attention, most errors come about in the diagnosis of malignancy when the condition is, in fact, innocent. This is of grave moment because both radical surgery and irradiation can cause devastating physical effects which often have far-reaching psychological consequences. However, irrespective of the differences of opinion regarding the relative merits of different forms of treatment, there is no disagreement concerning the necessity of early and accurate diagnosis.

Many types of histochemical methods have been studied in attempts to find a certain test for distinguishing the malignant cell from its neighbours, and thus clarify the present confused situation by removing uncertainty about many conditions which clinically and microscopically resemble carcinoma. None of these has proved satisfactory. This is easily understood when it is appreciated that all these methods depended on cytoplasmic qualities which may be widespread (such as hydrogen ion concentration) or localized (such as some special secretion). They did not provide a difference between neoplastic and non-neoplastic tissue. Notwithstanding the amount of work that has been done on the problem of the nature of malignancy, and despite the colossal amount of information obtained, results in the direction of our understanding of the possible fundamental changes involved have been relatively meagre.

Recently, however, experimental investigations in animals have suggested an approach to the problem which promises to be particularly fruitful, and the application of this to the naturally occurring tumours in man is discussed in this paper. It is of general importance, but special attention is given here to breast tumours.

HISTORICAL NOTE

Carcinoma of the breast was one of the earliest recognized tumours. That some of its general features were appreciated early is indicated by the use of the term 'cancer' over 2000 years ago. This term indicated that some aspects of its structure were understood and, as with other tumours, that it was regarded as some extraneous tissue growing on the body as a form of parasite.

In relatively recent times the concept of Cohnheim (1877) that tumours arise from segregated tissues helped to clarify the position at the end of the last century by separating the neoplasms sharply from other pathological conditions. However, this concept emphasized the view that tumours are, in some way, different from ordinary tissues.

Tumours have been observed frequently in animals, and some of these arising in the mammary glands of dogs and mice are frank carcinomata. Some of the tumours in mice are transmissible from one member of the same species to another by various means. A feature of one form of mammary cancer of one strain of mice is the transmission of some agent, the mammary tumour agent of the Bittner milk factor (Bittner, 1936), through the milk of the mother. This factor has the properties of an infectious agent or virus and has been used as an argument for the virus origin of tumours in general. There can be no doubt of the importance of this factor in some tumours in certain inbred groups of mice, but the nature of the process involved and the form of the agent responsible for this development are not yet clear. It seems probable that this is a sidetrack from the main highway of investigation of breast tumours.

The serological approach to the problem of tumour development, arising from the idea that the growth is something different from the rest of the body, developed strongly at the end of the last century. Much of this work was unproductive, but it has been continued in the experimental animal and, as might have been expected, has given most definite results in experiments with transplanted tumours. However, a new field has opened up recently with some liver tumours in rats.

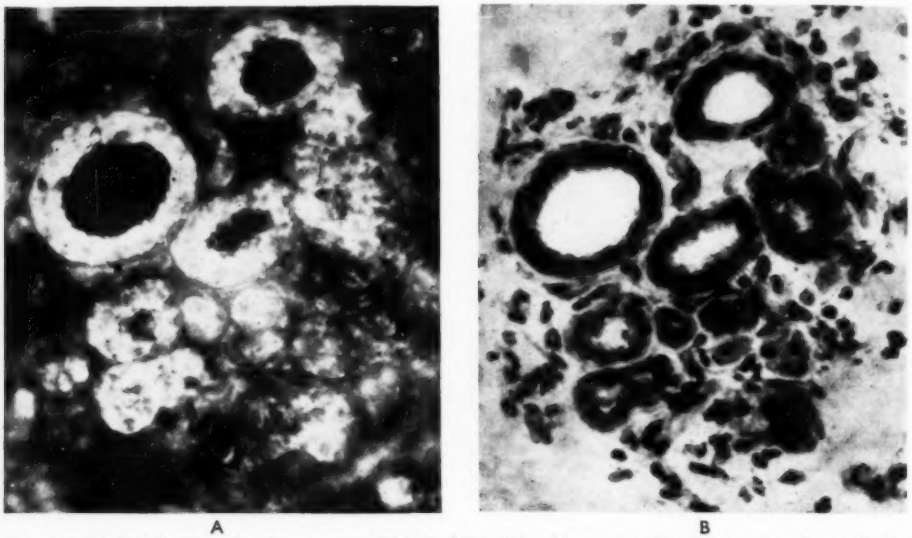
These tumours arise following the administration of butter yellow (4-dimethylaminoazobenzene). When fed to rats the dye becomes bound to certain proteins in the liver cells and, later, the tumours which develop can be shown to lack the capacity to bind the dye (Miller and Miller, 1947). This has been interpreted as being due to a deletion of the dye-binding protein(s). Loss of protein(s) of similar electrophoretic mobilities to these has been demonstrated by centrifugation of rat liver and rat hepatoma homogenates, and subsequent electrophoretic studies of the soluble proteins obtained (Sorof and Cohen, 1951; Eldredge and Luck, 1952; de Lamirande, Allard, and Cantero, 1953).

Antibodies are produced when homogenates of rat liver are injected into rabbits. The globulins obtained by fractionation of such a rabbit's serum have been found to react in complement-fixation tests with the cytoplasmic proteins of rat liver. This reaction may be visualized by first labelling the globulin with fluorescein isocyanate and observing the bright green fluorescence in ultraviolet light. When rat liver tissue is stained with this globulin-fluorescein complex, normal tissue stains well but tumour tissue does not (Weiler, 1956). This observation has been applied to liver tumours produced by many other carcinogenic azo dyes and, as well, to

tumours of the skin which follow the application of condensed polycyclic hydrocarbons.

Observations have been made also on the naturally occurring tumours of man. A group of tumours from various parts of the body have been investigated and, in all cases, a similar result has been obtained. A series of carcinomata of the colon has been specially studied (Louis, 1957 b) and, in all of these, the normal mucosa fluoresced, whereas the tumours did not.

One important feature has been the recognition that the basis of the demonstration of the characteristic staining by the globulin is independent of an antibody–antigen reaction (Hughes, Louis, Dineen, and Spector, 1957). Thus, simple globulin-fluorescein stains produce an effect similar to that obtained with a specific antibody globulin-fluorescein complex. This means that the reaction can be explained in a relatively simple physico-chemical basis and is not necessarily a complex biological phenomenon.



A B

FIG. 180.—Unfixed frozen section from a case of lobular hyperplasia of breast. A, Fluorescence photomicrograph showing fluorescence of all epithelial cells lining the ducts and acini and some of those in the stroma. B, Same area after fixation in formalin and staining with hæmatoxylin and eosin for comparison with A. (× 200.)

Table I.—THE VARIOUS BREAST TUMOURS EXAMINED BY THE FLUORESCEIN-GLOBULIN COMPLEX STAINING TECHNIQUE

CONDITION	NO. OF CASES	FLUORESCENCE
Lobular Hyperplasia	20	Bright and even
Cystic Hyperplasia	6	Bright and even
Adenosis	4	Bright and even
Fibro-adenoma	6	Bright and even
Carcinoma	35	Nil

N.B.—Carcinomas failed to fluoresce whilst all other tumours fluoresced brightly and evenly.

METHODS AND MATERIALS

1. Preparation of Sera.—Normal rabbit serum was fractionated by precipitation with half-saturated ammonium sulphate at 0° C. and the resultant globulin fraction was dialysed against phosphate buffered saline, *p*H 7·3, for two days, with daily changes of dialysate.

In earlier experiments 'organ specific' antisera were prepared by injecting rabbits with certain organ homogenates and then absorbing the antisera thus produced several times with acetone-dried fresh liver particles to remove non-specific antibodies. As it became apparent that the phenomenon was not a serological one (Hughes and others, 1957), this step in the procedure was omitted and equally specific results were obtained. This facilitated the application of this method to breast tissues.

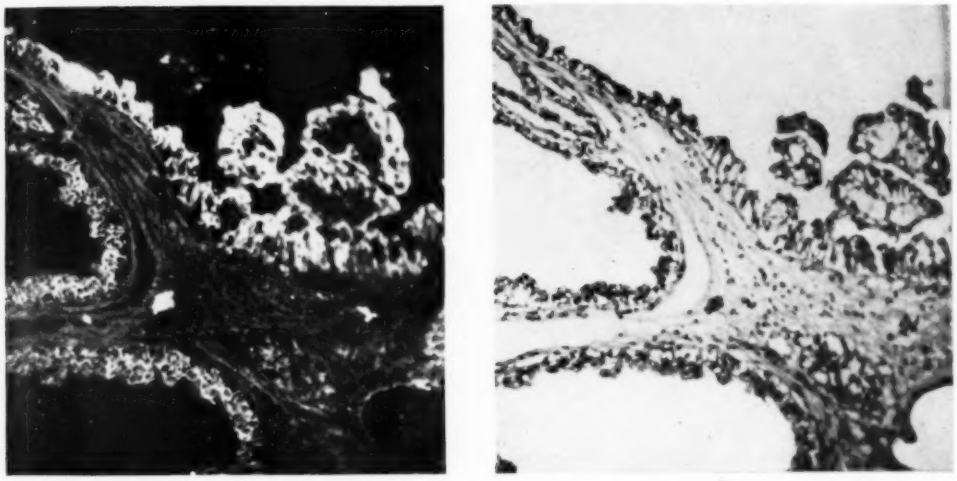
2. Labelling Globulin with Fluorescein Isocyanate.—The method used for labelling globulin with fluorescein was essentially that described in detail by Coons and Kaplan (1950). This fluorescein-globulin complex was dissolved in saline and dialysed for five days against phosphate-buffered saline, *p*H 7·6, to remove fluorescein derivatives, and the sera were stored in ampoules in a deep-freeze unit. Any remaining free fluorescein derivatives were extracted prior to use by absorption with ethyl acetate (Dineen and Ada, 1957).

3. Preparation of Tissue Sections.—Unfixed biopsy material was used in preparing tissues for sectioning. A small piece of tissue not more than 4 mm. thick was snap-frozen by dropping it in a tube of isopentane kept at −70° C. in a Dewar flask containing an ethanol–dry ice mixture. From these blocks unfixed frozen sections of 5–7μ thickness were cut at a temperature of −20° C. with a rotary microtome (M.S.E.), and placed in a deep-freeze

unit (Louis, 1957 a). The sections were picked up on ethanol-moistened slides, also at −20° C., and then transferred to a cold room at 0–2° C. and allowed to dry beside a fan for one and a half hours. These sections were again immersed in cold ethanol for a further fifteen minutes and dried in the cold room overnight.

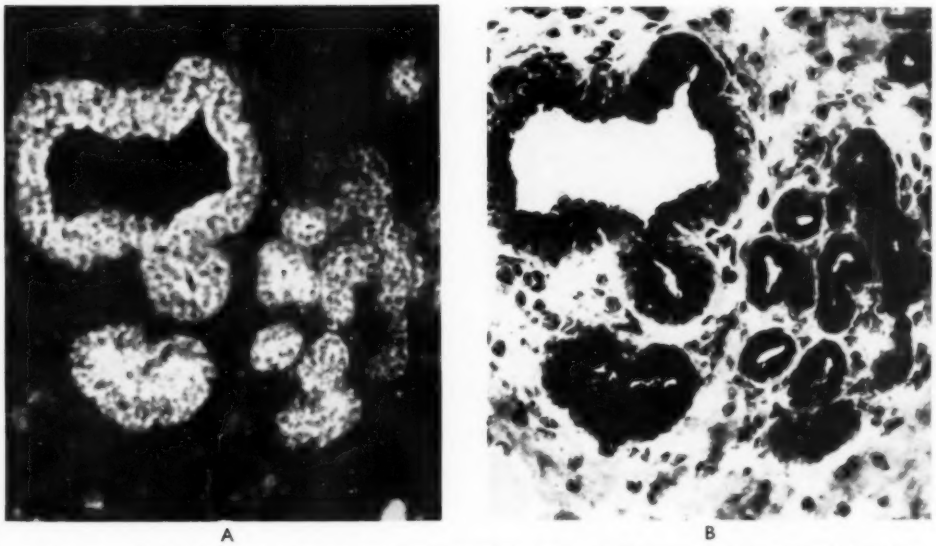
4. Staining of Tissue Sections.—The dried sections were treated with the fluorescein-labelled globulin for ten minutes at room temperature, washed gently for ten minutes in three changes of buffered saline, *p*H 7·3, and examined with a Leitz fluorescence microscope using ultraviolet light.

5. Microscopy and Photography.—A Leitz ultraviolet microscope with a carbon arc lamp as a source of light was employed. Between the light source and the condenser were placed two 4-mm. BG 12 filters, and in the eyepiece an ultraviolet protection filter 2·5 mm. (Euphos) and a Wratten G 15 gelatin filter. Pan F film (Ilford) was used for



A B

FIG. 181.—Unfixed frozen section from a case of cystic hyperplasia of the breast. A, Fluorescence photomicrograph showing fluorescence of all the hyperplastic and proliferating epithelial cells lining the cysts. B, Same area after fixation in formalin and staining with hæmatoxylin and eosin for comparison with A. (× 290.)



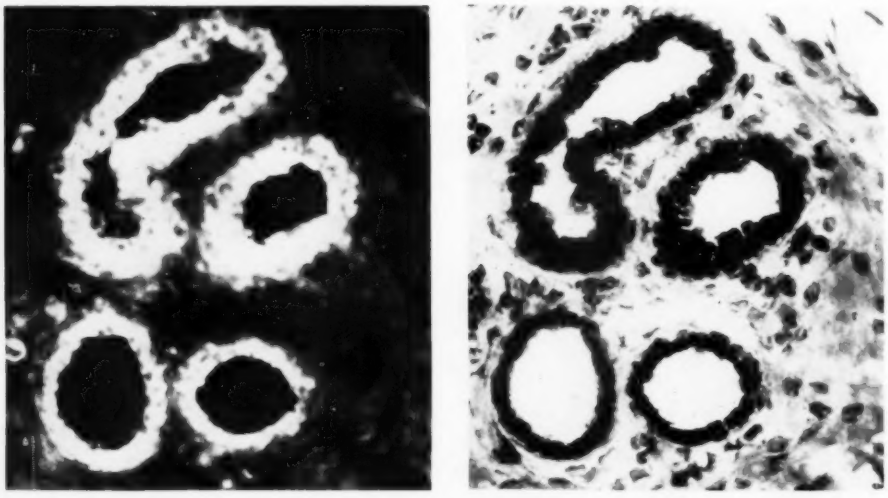
A B

FIG. 182.—Unfixed frozen section from a case of adenosis of the breast. A, Fluorescence photomicrograph showing a bright fluorescence of all the cells of the multi-layered epithelium lining the proliferating ductules. B, Same area after fixation in formalin and staining with hæmatoxylin and eosin for comparison with A. (× 200.)

photographic records with exposure times of 45 seconds.

Since the material is necessarily unfixed, disorganization of the tissues gradually occurs. Staining features with the fluorescein-globulin complex such as hæmatoxylin and eosin. For both reasons a record obtained by photography of the appropriate areas of the tissue is necessary.

In order to study particular areas adequately the following routine was employed in every case. The



A B

FIG. 183.—Unfixed frozen section from a case of an intercanalicular fibro-adenoma. A, Fluorescence photomicrograph showing bright fluorescence of all epithelial cells. B, Same area after fixation in formalin and staining with hæmatoxylin and eosin for comparison with A. (× 200.)

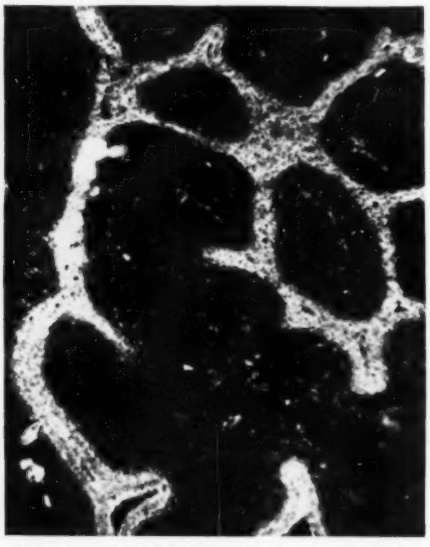


FIG. 184.—Unfixed frozen section from a case of intracanalicular fibro-adenoma stained with fluorescein-globulin complex and showing bright fluorescence of all epithelial cells. (× 120.)

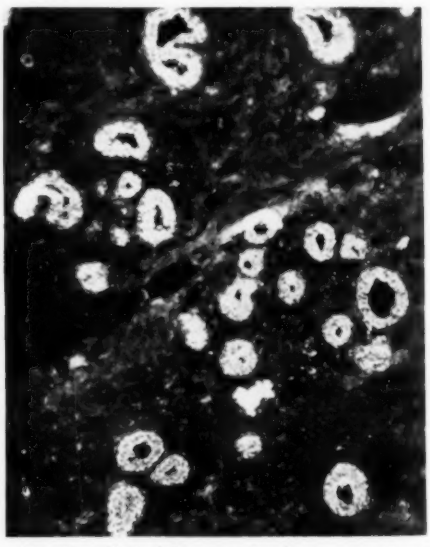


FIG. 185.—Unfixed frozen section from a case of pericanalicular fibro-adenoma stained with fluorescein-globulin complex and showing bright fluorescence of all epithelial cells. (× 120.)

are lost relatively quickly. Furthermore, it is necessary to compare the staining characters of the tissue by fluorescein with those by a routine stain sections were first examined with the fluorescence microscope and representative areas photographed. The same sections were then fixed in 10 per cent

formol-saline and stained with hæmatoxylin and eosin and, for comparison, the same areas were photographed again using visible light. Some sections which emitted considerable autofluorescence were examined with the phase-contrast microscope to select an appropriate area, then the same area was examined and photographed for autofluorescence prior to staining, and finally examined and photographed after staining for green fluorescence of the stain.

RESULTS

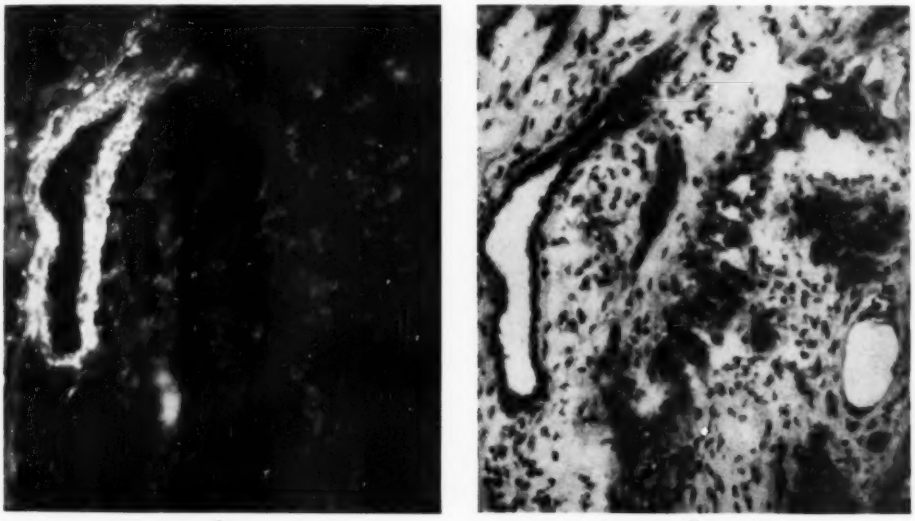
The fluorescence characteristics of normal breast tissues and those of the various breast tumours were investigated. In assessing the results attention was paid only to the green fluorescence of fluorescein. In the recognition of differential fluorescence a particular endeavour was made to have both normal and pathological tissues in the same microscope field and in such cases the loss of fluorescence was clearly demarcated at the margin of a carcinoma. In the case of carcinoma of the breast, however, it has been possible to find areas of tumour tissue surrounding breast-ducts (*Fig.* 186) or blood-vessels which served as controls for assessing differential staining.

The array of breast tumours examined by the method is depicted in *Table I*, and the results were recorded as to whether or not the epithelial cells emitted a bright green fluorescence.

1. Normal Breast Tissue.—Specific green fluorescence was emitted only by the epithelial cells lining the ducts and acini. In these cells the cytoplasm fluoresced brightly and evenly, whereas the nuclei did not, whilst in the stroma the background fluorescence of the periductal connective tissue was rather less than that of the general connective tissue of the breast proper.

2. Lobular Hyperplasis.—In all of the twenty cases of lobular hyperplasia which were investigated the epithelial cells of the ducts and acini fluoresced brightly (*Fig.* 180). The increased amount of periductal and periacinar connective tissue was evidenced by the stronger background fluorescence which diminished somewhat the contrast between the epithelial cells and stroma.

3. Cystic Hyperplasia.—Six cases of cystic hyperplasia were investigated and all showed a bright and even fluorescence of the epithelial cells. The tall columnar hyperplastic cells lining some of these ducts showed no diminution in brightness, while the compressed connective tissue stroma between these cystic spaces stood out clearly in the background (*Fig.* 181).



A B

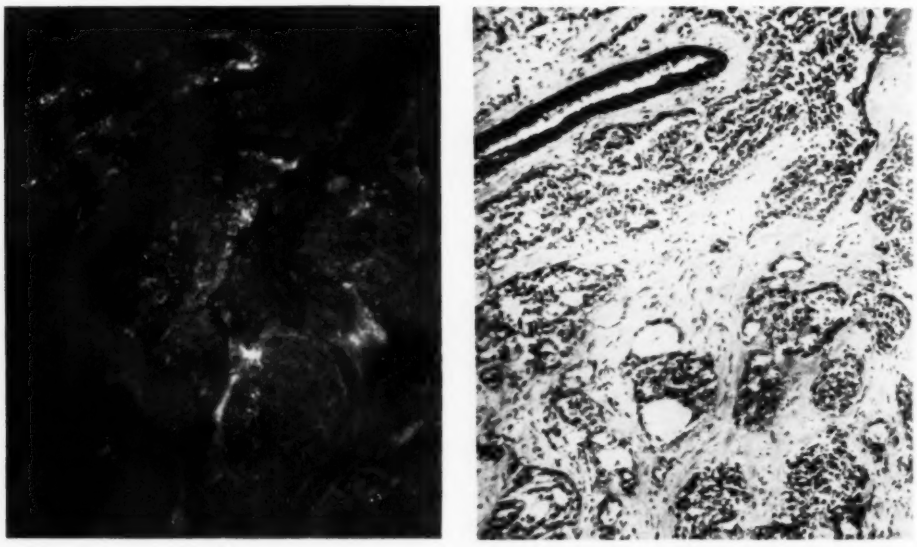
FIG. 186.—Unfixed frozen section from edge of carcinoma of breast. A, Fluorescence photomicrograph showing bright fluorescence of cells lining a duct and absence of fluorescence of remaining cells. B, Same area after fixation in formalin and staining with hæmatoxylin and eosin for comparison with A. The typical masses of carcinoma cells failing to fluoresce in A are apparent. The tumour is invading an area of the breast, a duct of which fluoresces well, in A by contrast with the carcinoma. (× 200.)

4. Adenosis.—Four cases of adenosis were investigated. All the cells of the multi-layered epithelium lining the proliferating ductules as well as the scattered epithelial cells in the surrounding connective tissue stroma fluoresced brightly (*Fig.* 182). There was no significant difference in the background between the periductal stroma and the general connective tissue stroma.

5. Fibro-adenomata.—Six cases of fibro-adenomata were investigated which included two examples of the intercanalicular type (*Fig.* 183), two examples of the intracanalicular type (*Fig.* 184), and two examples of the pericanalicular type (*Fig.* 185). In all cases the epithelium fluoresced brightly and the general background fluorescence was uniform throughout.

6. Carcinoma.—In all, 35 cases of carcinoma of the breast were investigated, of which the different

histological types are shown in *Table II*. The general findings in all cases were that all the epithelial cells within the histologically malignant areas failed to fluoresce in ultraviolet light (*Figs.* 186–188).



A B

FIG. 187.—Unfixed frozen sections from edge of carcinoma of the breast. A, Stained with fluorescein-globulin complex and showing complete loss of fluorescence; the autofluorescence of elastic tissue shows faintly. Note outline of islands of cells in background. B, Section, serial with A, after fixation in formalin and staining with hæmatoxylin and eosin for comparison. The hyperplastic duct does not fluoresce, in this region, any better than does carcinoma tissue. This phenomenon is comparable with 'loss of fluorescence' observed in 'precancerous state' elsewhere (*see* text). (× 160.)

Observation of sections selected from the peripheries of the tumours showed two types of duct:—

a. Those which fluoresced brightly and were surrounded by non-fluorescing groups or strands of malignant cells (*Fig.* 186), and

b. Those which failed to fluoresce (*Fig.* 187).

This latter type, after subsequent staining with hæmatoxylin and eosin, appeared histologically normal in that they were regular in outline, lined by a single layer of normal or hyperplastic cells, and these cells were sharply demarcated from the surrounding connective tissue stroma.

Table II.—THE DIFFERENT HISTOLOGICAL TYPES OF MALIGNANT TUMOURS EXAMINED. ALL FAILED TO FLUORESCE

HISTOLOGICAL TYPE	NO. OF CASES
Spheroidal cell	18
a. Scirrhus	
b. Encephaloid	10
Columnar cell	4
Mucoid carcinoma	1
Duct carcinoma	2

In addition to the human carcinomas of the breast, several breast cancers in animals were investigated. These included spontaneous breast tumours in mice (strain C3H), transplanted breast tumours in mice (strain C57), and spontaneous breast tumours in rats (Walker 265 carcinoma). In all of these the findings were similar to the human cancers in that the malignant tissues failed to fluoresce (*Fig.* 188).

DISCUSSION

The histological diagnosis of malignant tumours goes back to the middle of the last century. It has long been known that growths which present little or no difficulty macroscopically cause no dissension amongst histologists, yet there is a large group of doubtful 'tumours' where agreement is seldom achieved. Whilst information from follow-up series has greatly improved our understanding of some of these, there is still uncertainty about many others. The greater proportion of diagnostic difficulties encountered in the breast as compared with other tissues is probably due to its superficial position which enables early observation and easy removal.

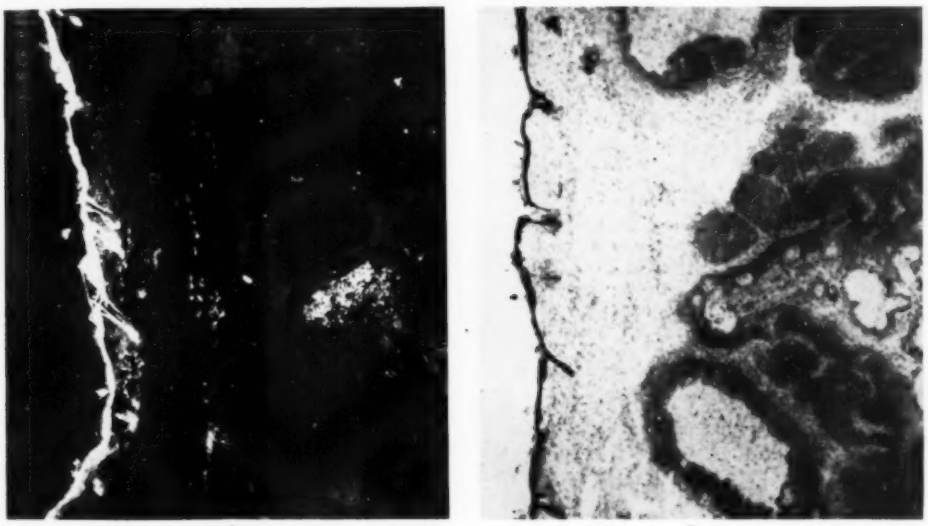
The problem of the distinction of hyperplastic conditions (chronic mastitis) from malignancy was recognized early, and good accounts, such as those of Bloodgood (1921) based on twenty years' experience, have emphasized the importance of recognizing the innocence of conditions which resemble carcinoma. Though some of the hyperplasias of the breast present no difficulty many of them show such extraordinary degrees of proliferation and deviation from the normal that they are continually recurring problems in their differentiation from

carcinoma. Not only may there be variations in cell size, variation in nuclear forms, increase in the number, size, variation in nuclear forms, increase in the number of cells lining the ducts, and increase in cell layers, but also the cellularity and atypicality of the tissue in general make the segregation of such areas from true neoplasms difficult. Furthermore, they are not infrequently associated with carcinoma when the difference between the tumour and the non-neoplastic tissue may be difficult to assess.

In cases of gross hyperplasia there is sometimes more than one area of malignant transformation. This raises the old question of the unicentric or multicentric origin of tumours. Whilst it is generally agreed that, from the viewpoint of the body as a whole, the unicentric origin of tumours is the rule, this does not necessarily apply within one tissue. Although experimental work and some clinical observations suggest that the presence of one growth inhibits the development of another, it is abundantly clear that a neoplastic change may occur in more than one part of some tissues. This is particularly well shown in some tumours of the skin. Thus the idea of a 'prepared field' in which the tumour arises has much to support it.

This is shown in some tissues by the methods described in this paper in areas of 'loss of staining'. It was first demonstrated in the rat liver after feeding with carcinogenic dyes where groups of cells failed to stain, and in these organs subsequently, hepatomas arose. Similar 'islands of loss' were demonstrated in man in tissues in which naturally occurring tumours either were arising or were known, by experience, to arise commonly. Such were the polyps of multiple polyposis of the colon.

In the present cases, examination of many examples of hyperplasia of the breast failed to show any such areas, although in a few cases where breast tissue was present adjacent to a frank carcinoma, some such areas were found. This phenomenon may well prove to be of first importance in some cases of gross hyperplasia in indicating that a true precancerous condition is present.



A B

FIG. 188.—Unfixed frozen sections from a spontaneous carcinoma of the breast in a mouse (strain C3H). A, Fluorescence photomicrograph of cells of epidermis and complete lack of fluorescence tissue to the right; some autofluorescence of wandering cells is apparent. B, Section serial with A fixed in formalin and stained with hæmatoxylin and eosin for comparison with A. (× 120.)

In many cases of tumour formation the diagnosis depends, largely, on invasion of surrounding tissues by the tumour. Indeed, this is an essential criterion for diagnosis of most neoplasms. In the normal hyperplasia of the organ (as in early lactation) there is invasion of the surrounding tissue and this is reproduced in many hyperplasias, in some of which the ducts grow out into the surrounding fat. The degree of differentiation of the ducts and regularity of the cells enables a distinction to be made, but some more specific feature is clearly desirable.

The forms of chronic hyperplasia, often designated by the older terms of chronic mastitis or cystic mastitis, vary greatly and these conform with various definite types referred to as simple hyperplasia, mammary dysplasia, cystic hyperplasia, adenosis, and the like. Some of these are clearly minor variants of the normal structure, differing only in the increase in the number of ducts. Others show greater variations, but can be recognized as aberrant proliferations with some clear relation to the hyperplasia associated with functional activity. Others still show gross degrees of proliferation with replacement of tissue and loss of the normal relationships. Retention of some organoid structure helps to distinguish them from frank neoplasms, but here also some specific means of differentiation is desirable.

A difficulty which is found in other organs, such as in the thyroid, is the innocent tumour—the fibro-adenoma. The well-developed example is the encapsulated mass which, microscopically, is

composed of numerous ducts arranged in various forms indicated by the terms inter-, peri-, and intra-canalicular types. They all have a regular appearance indicating their innocence, and they are sufficiently different from the ordinary breast tissue to suggest that they may be neoplasms. Some features raise doubts as to their nature. This type of structure is found sometimes scattered through a breast showing diffuse or lobular hyperplasia, it retrogresses and disappears just as do areas of hyperplasia and, occasionally, progressive and invasive types are found.

The manner in which these nodules have stained by the method employed here suggests that they are not neoplasms, at least as far as the chemical features of the cytoplasm of malignant tumours is concerned.

The importance of the assessment of the observations in fluorescence microscopy in surgical biopsies needs little emphasis. Ordinarily the diagnosis of conditions by frozen sections using ordinary stains presents difficulties in the very type of case in which most help is required. In the macroscopically typical example the histological diagnosis is easy, but difficulty in the assessment of gross appearances is paralleled by difficulty microscopically. It is in such conditions that an irrefutable technique is particularly useful and desirable.

The significance of the observations recorded in this paper relates both to fully developed frank tumours and to incipient tumours, that is, the precancerous state. The distinction between a neoplasm and normal or hyperplastic tissue is clear cut and definite.

Failure of groups of cells to stain has been observed, as mentioned earlier, in animal organs in which tumours are developing or, as shown by observation of a large series, about to arise. Furthermore, they have been seen in polyps of the large intestine associated with carcinoma. Comparable areas have been few and small in size in the specimens of breast examined in this series. This is well shown in a hyperplastic duct in a scirrhus carcinoma in *Fig.* 187. Their presence, however, in polyposis coli helps to orientate this condition in relation to the development of carcinoma which occurs more often in these than it does in hyperplasias of the breast.

There are many problems of carcinogenesis, for example, relating to precancerous states, 'prepared fields', degree of activity of carcinogens, and many others which may be studied by means of this method.

As was indicated earlier, it has always been assumed that tumour tissue was in some way different from other tissues in the body. Indeed, this has been the basis of much investigation over the last half-century, and the view that an antigen–antibody reaction was responsible for the characteristic histochemical differences recorded here was related to this idea.

The phenomena described are due to a difference between cells which are, but for one feature, essentially the same. Although it has been generally thought that tumour cells possess some features not present in normal cells, it is clear that they differ from them in that they lack a protein complex found in normal tissue. It is this loss which constitutes mutation of the cells (or at least part of it) when they become neoplastic.

The earlier explanation of the phenomenon was that an antibody was produced to this protein so that a reaction could be demonstrated with the cell containing it (the normal cell), but not with the cell lacking it (the neoplastic cell). However, the successful use of sera from animals not injected with normal tissue demonstrates that the difference in staining, as illustrated here, is due to a physico-chemical phenomenon (a coalescence of two differently charged proteins) independently of any serological attributes.

This has been of special importance in dealing with breast tissue because, at the stage where the problem was being studied from the viewpoint of antibody γ-globulins, it was found difficult to obtain breast duct (or alveolar) epithelium in sufficient quantity to provide satisfactory material for injection as an antigen. The observation that a simple globulin complex is as efficacious as a stain as a presumably specific γ-globulin has disposed of one of the serious technical difficulties.

SUMMARY

A study of tumours of the breast has been made using a staining technique by which a clear distinction can be made between normal and malignant cells.

It has been shown, by using a globulin-fluorescein complex stain, that normal tissue cells, mainly of epithelial type, stain well (and can be demonstrated by fluorescence in ultraviolet light), but cells of malignant tumours do not.

Hyperplastic tissues and those of fibro-adenomata of the breast show the same features of normal tissue and thus are clearly distinguishable from neoplastic tissue.

These observations have been developed from those made in experimental cancer research work where normal rat liver stained well with rabbit globulin-fluorescein but hepatomata arising from feeding with butter yellow did not.

This method has been applied to naturally occurring tumours in man (as well as animals) and the same distinction between neoplastic and non-neoplastic tissues has been observed uniformly.

The method began to be employed as an antigen-antibody reaction; globulin obtained from animals that have been injected with appropriate tissue was used as an integral part of the stain. Since it has been shown that a similar result is obtainable using a simple globulin fraction from any rabbit this simplification of the technique has been employed here.

Acknowledgements.—My thanks for making material available are due to members of the surgical and pathological staffs of the Royal Melbourne and Alfred Hospitals and, particularly, to Messrs. G. R. Syme, E. S. R. Hughes, T. H. Ackland, and S. F. Reid for material from private cases.

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RUPTURE OF CHOLEDOCHAL CYST DURING CONFINEMENT

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SINCE Vater first described the condition of choledochal cyst in 1723, 202 cases have been reported in the literature. Reviews by Shallow, Eger, and Wagner in 1946 of 175 cases, and Attar and Obeid in 1955 of 201 cases, deal with the subject very fully, and in 1957 Serfas and Lyter added a further case.

Aird (1949) estimates that the condition is found in approximately $\frac{1}{200}$ of one per cent of operations on the bile passages, and $\frac{1}{11000}$ of autopsies. The case to be described here was diagnosed after rupturing during confinement, a complication which is not mentioned in the reviewed literature.

CASE REPORT

Mrs. R. M. C., aged 27 years, was first seen on Nov. 9, 1956, with a history of three attacks of epigastric pain in the past year. Each attack began with central epigastric pain with vomiting, which after twenty-four hours became localized to the right costal margin for a further day or two. There had been no jaundice or colour changes in urine or fæces. On examination nothing abnormal was detected beyond some tenderness along the right costal margin, and no mass was palpable.

A cholecystogram had recently shown a normal functioning gall-bladder with no calculi present. A biligrafin examination was then performed, which showed

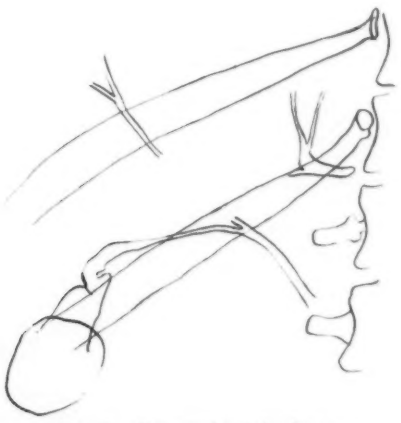

FIG. 189.—Pre-operative cholangiogram.

a normal common duct and dye in the duodenum within twenty minutes.

Shortly after this the patient became pregnant, and was not seen again until Sept. 17, 1957, approximately two weeks after the confinement. Throughout the pregnancy she had been well apart from a short episode of anorexia, nausea, and some epigastric pain associated with mild jaundice, which her attendant practitioner had regarded as infective hepatitis. Following childbirth she developed upper abdominal pain with vomiting, and jaundice after several days. Liver function tests at this stage indicated an obstructive jaundice.

On examination on Sept. 17, 1957, she was dehydrated, drowsy, febrile, and moderately jaundiced. A large tender mass about the size of a cricket ball was easily palpable below the right costal margin through her lax abdominal wall. After restorative intravenous therapy

and vitamin K administration laparotomy was performed on Sept. 25, 1957.

This disclosed a large cystic swelling in the right upper quadrant. The wall was formed by adherence of colon and adjacent viscera, and on separation this was found to contain a ruptured choledochal cyst and free bile. The cyst lay partially within the liver, protruding from its inferior surface, but no communication with the

biliary tract was demonstrable. As the patient's general condition did not permit further exploration a drainage tube was inserted into the cyst cavity and the wound closed.

Following this her jaundice subsided, and she made a good recovery, draining 15 oz. of bile daily from the tube. The fæces returned to normal colour, and she gained weight. On Oct. 14, 1957, some thin lipiodol was injected down the tube, outlining a cavity about the size of a golf ball, but showing no communication with the bile-ducts.

On Nov. 8, 1957, further surgery was undertaken, and the cyst was anastomized to a Roux-Y loop. The cyst was found to emerge from the inferior surface of the liver, lateral and posterior to the gall-bladder, which was collapsed and normal in appearance, but its communications within the liver and porta hepatis were still obscure. The common duct was narrow but of normal appearance. The common hepatic ducts and porta hepatis were overlaid by, or possibly incorporated in, the cyst wall and not visualized, but it was thought that the cyst communicated with the right hepatic duct in view of its position. The cyst wall was thickened, and the lining almost polypoidal in appearance. Excess cyst wall was excised, and choledochocystjejunostomy in Roux-Y performed, using a long antiperistaltic loop, after partial closure of the cyst to equalize the jejunal lumen. Convalescence was uneventful, and the patient left hospital on the fourteenth day after the second operation and has remained well since.

DISCUSSION

A choledochal cyst is a localized dilatation or enlargement of the biliary tree which, characteristically, is limited to the supraduodenal portion of the common duct. Less commonly it may arise from the common hepatic duct with the cystic, right, and left hepatic ducts entering as separate ducts, separated by cyst wall. The cyst wall is usually thick, and microscopically is characterized by fibrous tissue

FIG. 190.—Post-operative cholangiogram.

from which the mucosa of the cyst wall has usually been denuded.

The condition is considered congenital in origin, the most tenable theory being that the cyst is the result of a congenital weakness of the duct wall, which can dilate under normal pressures. In some cases this may be associated with partial obstruction due to stenosis secondary to cholangitis or other abnormality (Serfas and Lyter, 1957). It occurs predominantly in young females, 75 per cent being below the age of 25 years in the 202 cases reviewed by Attar and Obeid (1955).

Aird (1949) states that pregnancy precipitates or exaggerates the condition, as in this case, and it is probable that enlargement of the cyst occurred during pregnancy, following changes in intra-abdominal pressures and relationships, and heralded by an attack of cholangitis which was thought to be infective hepatitis.

The previous three mild attacks of upper abdominal pain, which clinically resembled acute cholecystitis, may well have been mild cholangitis which did not produce sufficient obstruction to precipitate enlargement of the cyst.

Rupture presumably occurred during the strain of labour, when the pain produced would pass unnoticed. Fortunately, the surrounding viscera formed a secondary cyst wall and prevented general biliary peritonitis. The diagnostic triad of jaundice, abdominal pain, and right upper abdominal tumour presented after a few days or so.

The exact relationship of the cyst to the hepatic ducts could not be determined without endangering the patient, but from its immediate relations it was assumed that it arose from either the common

hepatic duct or the right hepatic duct. The amount of bile drainage indicated communication with a large duct, and yet a reasonable quantity of bile was able to pass to the duodenum, as evidenced by the return of the fæcal colour to normal.

A comparative study of the pre-operative and post-operative cholangiograms seems to confirm the opinion that the cyst arose from the junctional area, involving mainly the right hepatic duct and incorporating the left and common hepatic duct to a lesser extent.

Fig. 189 shows a well-defined cystic and common bile-duct, with short segments of the left and right hepatic ducts. The junctional area is not outlined.

In *Fig.* 190 this area is seen more clearly, and is obviously abnormal. The left hepatic duct seems relatively normal, but the right hepatic duct appears considerably dilated. This diffuse enlargement represents the anastomotic area and the remnant of the cyst, and a gas bubble is seen in the jejunum nearby, marked X.

Treatment.—In reviewing the reported 202 cases, Attar and Obeid (1955) found that external drainage of the biliary system, with or without excision of the cyst, carried a high mortality (85–90 per cent) because of the associated complications of biliary fistula and bleeding due to vitamin-K deficiency. Aird (1949) states that death has invariably followed drainage of the cyst to the surface.

In this patient initial external drainage was resorted to as the only feasible procedure in a very ill patient, and resulted in rapid improvement in her general condition.

They also found that anastomosing the cyst to the duodenum carried a mortality of 24 per cent, and was complicated by post-operative cholangitis in 12 per cent.

Choledochocystjejunostomy in Roux-Y, performed in 9 cases with no mortality or cholangitis, was found to be the best procedure.

An antiperistaltic loop of 30 cm. of jejunum is used, as advised by Pearse, Radakovich, and Coghill (1949), which minimizes the risk of regurgitation of food into the biliary tree.

A wide stoma is advisable, as Walters (1945), in reviewing 186 cases of stricture of the common and hepatic bile-ducts, concluded that cholangitis is not secondary to the reflux of gastro-intestinal contents, but to obstruction at the site of anastomosis.

SUMMARY

A case of choledochal cyst in a woman aged 27 years is presented. Rapid enlargement in its size during pregnancy was followed by rupture during confinement.

Treatment by initial external drainage followed by anastomosis of the cyst to a Roux-Y loop of jejunum was successful, and has not been followed by cholangitis or other complications.

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EXPERIMENTAL SURGERY

THE EXPERIMENTAL PRODUCTION OF GASTRIC ULCERS BY HISTAMINE-RELEASING SUBSTANCES

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MACINTOSH and Paton in 1949 described a group of substances which have the property of releasing histamine in the tissues, and are known as histamine liberators. They act by releasing the tissue histamine into the circulation. Subsequently, attempts have been made to reduce the histamine in the tissues of various species by repeated injections of histamine liberators and to study whether this altered in any way phenomena in which, in the past, histamine had conjecturally been assigned a possible role. It has been shown, for example, using such a technique of repeated injection until the normal tissue histamine stores are depleted, that histamine is necessary for the erythema and œdema reaction of photosensitivity. In histamine-depleted rats the injection of hæmatoporphyrin followed by exposure to ultraviolet light is almost entirely without effect. Similar pre-treatment of rats with a histamine liberator confers an immunity to the œdema reaction induced by the injection of a foreign protein such as egg albumen (Feldberg and Talesnik, 1953).

In the present study histamine release has been examined in two species. It was found to be of some magnitude in rats, but was, in contrast, of a much lower order in guinea-pigs. Nevertheless, enough histamine is set free in both species to cause the

development of gastric ulcers. Various agents or extracts have been described which have been thought to induce gastric ulcer specifically, before or after sensitization of the animal to them. It is now shown that gastrotoxin in guinea-pigs and horse serum in rats, which were formerly thought to induce a specific form of gastric ulcer, do so in virtue of their common property of histamine release. These sera and toxins may be without effect when preceded by moderate doses of histamine liberators planned to release the tissue histamine gradually; loss of the tissue histamine annuls the effect of the sera and toxins and tends to support the argument that they act via histamine release.

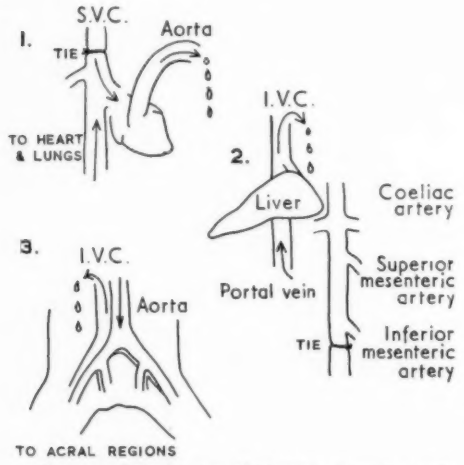


FIG. 191.—Perfusion areas of guinea-pig. Areas 1, 2, and 3 were perfused after cannulating the inferior vena cava, cœliac artery, and aorta respectively. The effluent was collected from the aorta and inferior vena cava supra-diaphragmatically and infra-diaphragmatically respectively.

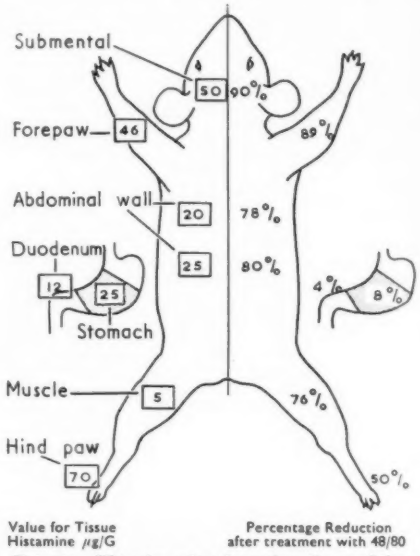


FIG. 192.—Histamine values for various tissues of the rat are listed (left); the effect of histamine liberation by Compound 48/80 is to diminish tissue histamine as indicated (right); average of three experiments.

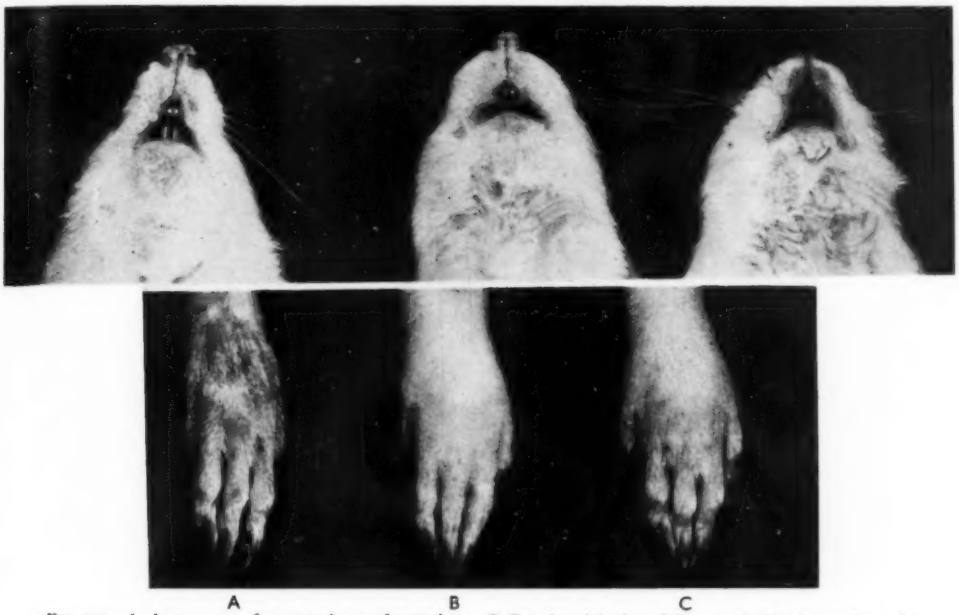
METHODS

Albino guinea-pigs (180–220 g.) were injected intraperitoneally, subcutaneously, and intravenously into veins on the extremities, with Compound 48/80 (Burroughs Wellcome), a potent histamine liberator (Paton, 1951). Albino rats were chosen and treated for histamine depletion by the serial injection technique of Feldberg and Talesnik (1953). Tissue extracts were made as described by Smith (1953) and were assayed for histamine on the atropinized guinea-pig's ileum. Blood for plasma-histamine determinations was obtained by exsanguination of the animal from the severed jugular veins into a siliconed vessel, containing 0·02 mg./ml. heparin. The blood was then centrifuged at 2000 r.p.m. and the supernatant tested on the guinea-pig's ileum before and after addition of mepyramine to the bath. Many of these determinations were controlled, extracting the tissues by classical techniques such as Code's (1937) modification of the method of Barsoum and Gaddum (1935).

In perfusion experiments the animals were anæsthetized with 25 per cent urethane 6 ml./kg. and perfusion experiments were carried out with Locke's solution through which was bubbled O_2 and CO_2. The perfusion cannula was inserted into the supra-diaphragmatic inferior vena cava for the lung perfusion, and the superior vena cava and the azygos veins were tied; effluent was collected from a cannula in the aorta, from both lungs and the heart in situ. Similarly, by insertion of the perfusion cannula in the upper part of the abdominal aorta, and by tying its lateral branches to the abdominal wall and urinary tract, with further ligation of the aorta at its termination, the alimentary tract and liver could be perfused in situ by inserting the cannula to collect the effluent from the hepatic veins in the supra-diaphragmatic portion of the inferior vena cava; ligation of side vessels of the vena cava and iliac veins was also performed. The tissues of the lower extremities were perfused by inserting the cannula in the lower abdominal aorta and collecting the effluent from another cannula tied into the origin of the inferior vena cava (*Fig.* 191).

Subcutaneous injections of Compound 48/80 were made in guinea-pigs under the shaved skin of the abdomen in volumes up to 0·5 ml. (concentrations of 1 : 500 and 1 : 1000). Intraperitoneal injections were likewise given using this volume, in all but one group of experiments where the volume was increased up to 5 ml. (1 : 10,000 solution). Histamine liberator was also dispersed in a slow release medium consisting of peanut oil with the addition of beeswax as described by Bruce and Parkes (1952). Antihistamine was given as mepyramine maleate. For the purpose of sensitization, horse serum was administered subcutaneously (0·5 ml.) and the antigen repeated 14 days later: 0·2 ml. or 0·5 ml. was now injected and the time of onset and severity of symptoms noted (this dose was repeated,

if necessary, since the amount of antigen required to produce anaphylaxis varies somewhat). For primary injection in rats, without prior sensitization, 1 ml. horse serum was injected; this was compared with the effects of 200 μg. Compound 48/80. Aminoguanidine was injected in 1 mg./kg. dosage as the and erosion (*Fig.* 194 B, C compared with F, G), and indeed perforation may be produced (*Fig.* 194 H). The effects of horse serum are less dramatic (*Fig.* 194 B, C) than after Compound 48/80 (*Fig.* 194 F, G) but are greater during treatment by the anti-histaminase agent, aminoguanidine (*Fig.* 194 D).



A B C

FIG. 193.—A, Appearances of snout and paw of normal rat. B, Rat given injection of Compound 48/80 intraperitoneally with consequent œdema at both sites. C, Comparable appearances after injection of horse serum.

sulphate. Gastrotoxin was prepared as described by Bolton (1904); 10 ml. were injected intraperitoneally into guinea-pigs and the tissue examined for gastric ulcers (Bolton, 1908) by standard histological methods.

RESULTS

1. Histamine Release and Gastric Ulcers in the Rat.—Feldberg and Talesnik (1953) have described the effects of Compound 48/80 in the rat. They found a marked reduction of tissue histamine, confirmed in the present experiments (*Fig.* 192), the values for the gastro-intestinal tract showing a much smaller change than the other tissues; they detected the release into the plasma of large amounts of histamine. The general effects are those of prostration, erythema, and œdema (*Fig.* 193 A, B). These effects are duplicated entirely by horse serum (*Fig.* 193 C) which acts as a primary histamine-releasing agent in the rat and does not require the agency of prior sensitization (Schachter and Talesnik, 1952). The plasma values for histamine after 200 μg. Compound 48/80 and 1 ml. horse serum are high, highest when the agents are given systematically, and most of all when enzymatic destruction by histamine is prevented by the anti-histaminase, aminoguanidine (Schayer and Smiley, 1954; *Table I*, A). The effects on the stomach closely parallel the histamine values; the greater the histamine values the higher the incidence of ulceration The most severe effects of all follow administration of Compound 48/80 and aminoguanidine (*Fig.* 194 H). Prior treatment with Compound 48/80 resulted in a release of histamine from many tissues, as is shown in *Fig.* 192. Subsequent attempts to provoke the typical effects of horse serum (*Fig.* 194 B, C, D) were ineffective (*Fig.* 194 E).

Table I.—VALUES FOR PLASMA HISTAMINE

AGENT	ROUTE OF ADMINISTRATION	HISTAMINE (μg./ml.)	
		A	B
Normal values		0·02	0·005
Compound 48/80	Local, subcutaneous	0·03	0·005
	General, intraperitoneal	0·8	0·24
	General + aminoguanidine	1·2	0·31
Horse serum	Local, subcutaneous	0·02	0·005
	General, intraperitoneal	0·05	0·17
	General + aminoguanidine	0·06	0·28

Values for the plasma histamine: (A) In the rat after 200 μg. Compound 48/80 and 1 ml. horse serum. (B) In the guinea-pig after 4 mg./kg. and 0·5 ml. horse serum repeated after 10–14 days' interval (in each case average of 3 experiments).

2. Evidence for Histamine Release in Guinea-pigs.—In guinea-pigs there is little information available on the effects of histamine liberators

on tissue histamine. Mongar and Schild (1952) in experiments with Compound 48/80 *in vitro* found as much histamine released as by the antigen–antibody reaction in sensitized tissues. On the other hand, Compound 48/80 injected intraperitoneally or intravenously was found by Mota and Vugman

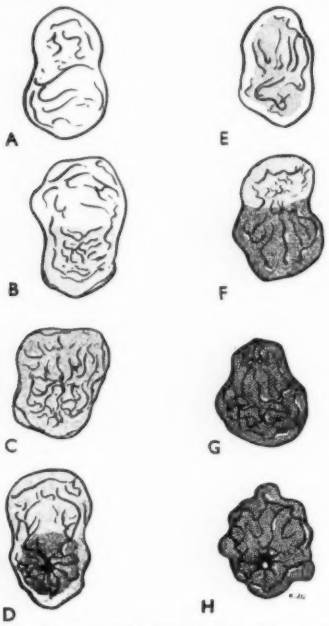


FIG. 194.—Diagrammatic representation of rat stomach which normally consists of upper epithelial sac and lower secretory portion. The density of stippling is an attempt to represent mucosal congestion as appearing on colour photographs from 3 animals treated in each group. Same dose as in *Table I*. A, Normal stomach. B, After horse serum locally subcutaneously. C, After horse serum intraperitoneally. D, After horse serum + aminoguanidine. E, After horse serum intraperitoneally (previous injections of Compound 48/80 to deplete labile histamine). F, After Compound 48/80 locally subcutaneously. G, After Compound 48/80 intraperitoneally. H, After Compound 48/80 + aminoguanidine.

(1956) to cause little diminution of histamine in the tissues. Nevertheless, they described the appearance of many effects attributable to histamine entering the circulation such as have been observed in the present experiments, for example, vasodilatation in the ear and prostration with respiratory effects. Evidence that there is a release of histamine from the tissues was obtained as follows.

a. Appearance of Histamine in the Plasma.—Guinea-pigs injected intraperitoneally with 10 mg./kg. Compound 48/80 and showing signs of histamine poisoning within 15–30 minutes had appreciable amounts of histamine-like substance present in the plasma (*Table II*). The activity of the substance was probably that of histamine since the contractile effect of both was abolished by mepyramine; furthermore, the return of the response to the active substance paralleled that of histamine when all mepyramine had been washed out of the bath (*Fig.* 195).

b. Release of Histamine from Perfused Tissues.—To ascertain the origin of the released histamine various tissues and organs were perfused. Feldburg and Talesnik (1953) have shown that histamine release in the rat occurs principally in such tissues as skin and skeletal muscles. In the guinea-pig, however, the histamine content of the skin is conspicuously low (*Fig.* 196), the values for the abdominal

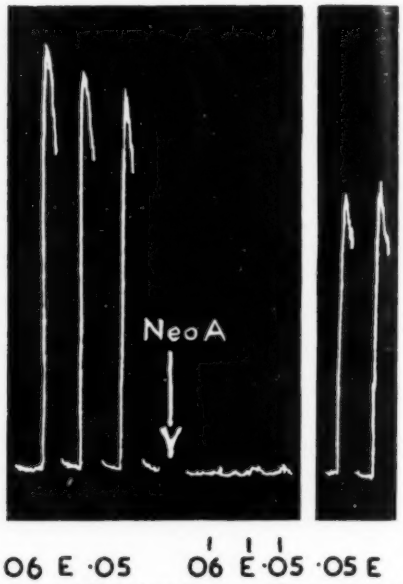


FIG. 195.—Effect of 0·06 and 0·05 μg. histamine on guinea-pig's ileum preparation, set up in tyrode solution in 20 ml. bath. At E, 0·2 ml. extract of plasma was given. At arrow 0·4 μg. neo-antergan (mepyramine) added to bath abolishes the contractile effects. The final contractile effects of the extract and of 0·05 μg. histamine were obtained after repeated emptying and refilling of the bath to remove all traces of neo-antergan (mepyramine) (atropine 1 : 500,000 solution added in 0·2 ml. solution throughout).

skin ranging from 3·2 to 9·9 μg./g. in the present experiments. There are, however, small areas of higher histamine content such as the skin of the ear, the submental region, the genital, nipple, basal, and

Table II.—PLASMA HISTAMINE

TIME AFTER INJECTIONS (mins.)	SYMPTOMS	PLASMA HISTAMINE (μg./ml.)
15	Prostration	0·24
15	Prostration	0·38
25	Shock	0·5
30	Shock	0·5
Control	—	0·005
Control	—	0·005

Plasma histami ne μg./ml. of 4 guinea-pigs after 10 mg./kg. Compound 48/80 intraperitoneally. As indicated, the animals were killed when seriously affected.

orbital regions. On the other hand, in this species other distinct tissues such as lung and intestine are particularly rich in histamine and yielded values on extraction ranging from 42 to 23 μg./g.

Table III lists the values for histamine output after arterial injection of Compound 48/80 into the thoracic and abdominal visceral organs and into the lower extremities. Only when skin and skeletal muscle are perfused is there a substantial release of

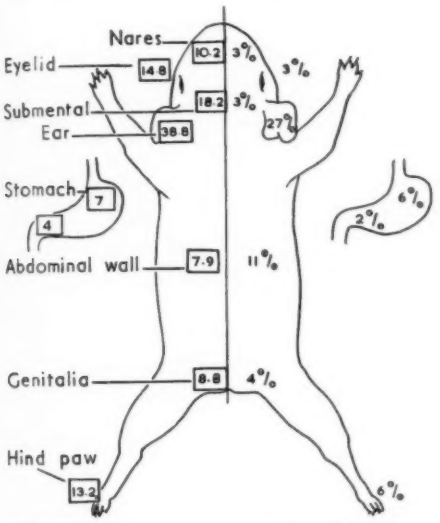


FIG. 196.—Histamine values for various tissues of the guinea-pigs are listed (left); the effect of histamine liberation by Compound 48/80 is to diminish tissue histamine to the small extent indicated (right). (Average of three experiments.)

histamine, the output from the lungs and gastro-intestinal tract being of a much lower order. Vaso-constriction with temporary reduction in perfusion flow accompanied the release of histamine; intestinal peristalsis and distension of the lumen with secretion was observed after injection of Compound 48/80 into the perfused intestine.

c. Reduction in Tissue Histamine following Intravenous and Intraperitoneal Administration of Compound 48/80.—Following the injection of substantial

Table III. HISTAMINE OUTPUT

DOSE IN MG.	HISTAMINE OUTPUT (μG./ML.)		
	T	A	E
0·5	1·2	0·8	16·4
1·0	1·8	1·7	21·5
2·0	2·2	1·9	28·3
2·0	2·6	2·4	30·4

Histamine output (μg./ml.) in perfusate from thoracic viscera (T), abdominal viscera (A), and lower extremities (E), after various doses of Compound 48/80.

amounts of Compound 48/80 into guinea-pigs there was only a slight reduction of tissue histamine. The animals treated intraperitoneally showed a slightly greater reduction in the histamine of their tissues than the animals treated by immediate intravenous injection (*Table IV*, *Fig.* 196).

Several measures were adopted to modify the toxic action of Compound 48/80 which may have been the result of the sensitivity of this species to released histamine or to the toxic effects of the compound itself. This was evident as prostration,

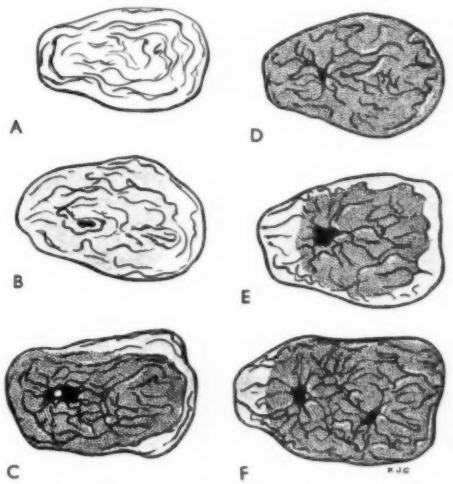


FIG. 197.—Diagrammatic representation of guinea-pig's stomach. The density of stippling is an attempt to represent mucosal congestion as appearing from colour photographs from 3 animals, so treated in each group. A, Normal stomach. B, After Compound 48/80 intraperitoneally. C, After Compound 48/80 + aminoguanidine. D, After anaphylactic shock with horse serum intravenously. E, After Bolton toxin (gastrotoxin intraperitoneally). F, After Bolton toxin (gastrotoxin) intraperitoneally + aminoguanidine subcutaneously.

respiratory embarrassment, and, on post-mortem examination, gastric ulcers of the acute type. The gastric ulcers and erosions were more pronounced with the combination of Compound 48/80 and aminoguanidine (*Fig.* 197 B, C). To diminish the intensity and yet permit prolonged action Compound 48/80 was administered by intraperitoneal and sub-

Table IV.—REDUCTION IN HISTAMINE

CONTROL VALUES (μG./G.) FOR HISTAMINE OF SKIN REGIONS		PERCENTAGE REDUCTION AFTER COMPOUND 48/80		
		A	B (4–6 days)	C (10 days)
Ear	38·8	27	32	39
Submental	18·2	3	7	14
Abdomen	7·9	11	13	33
Paw	13·2	6	6	13
Eyelid	14·8	3	5	—
Nares	10·2	3	3	10
Genitalia	8·8	4	3	7

Reduction in skin histamine after treatment with Compound 48/80: (A) average values after intravenous injections (1·5–2·5 mg./kg.); (B) of animals examined after 4–6 days and (C) 10 days of intraperitoneal injections (total dose administered 20 and 46 mg./kg. respectively; average of three experiments).

cutaneous injections dissolved in a large bulk of saline or dispersed in a slow-release medium; in another group, histamine intoxication was avoided by antagonizing the released histamine with an

antihistamine compound such as mepyramine. With none of these methods was it possible to get as marked a depletion of histamine as with rats, and there was little reduction in the rich stores of visceral histamine (*Table V*). Comparison of the groups of animals treated over three weeks with Compound 48/80 shows that the histamine values are lowest for

Table V.—Reduction in Histamine

	Control Values μg./g.	Percentage Reduction after Compound 48/80 (Total Dose 68 mg./kg.) 1	2	3	4	Antigen–antibody Reaction 5	Bolton Toxin (Gastrotoxin) 6
Skin, ear	36·6	21	27	15	46	50	16
Abdomen	7·6	19	16	5	38	48	12
Skeletal muscle	4·1	16	17	1	28	31	6
Lung	38·4	2	9	1	36	33	10
Intestine	26·2	4	8	2	10	10	8
Plasma μg./ml.	0·01	—	—	—	—	0·52	0·38

Reduction in histamine after treatment with Compound 48/80 over three weeks with: (1) Subcutaneous injections; (2) Intraperitoneal, in 5 ml. saline; and (3) Dispersed in oily medium; (4) 5–25 mg./kg. mepyramine; (5) 0·5 ml. antigen in animals sensitized with horse serum; (6) Injection of Bolton toxin (gastrotoxin). (1–6 are the average values from groups of 8 experimental animals.)

the mepyramine-injected group of animals. This may be accounted for by the enhanced release of histamine in the tissues, since mepyramine has itself the actions of a strong histamine liberator (Arunlakshana, 1953).

3. Comparison of the Effects of Compound 48/80, Gastrotoxin, or 'Bolton Toxin' and Sensitization.—Eight guinea-pigs were treated with Compound 48/80 intraperitoneally in 5 ml. saline as in *Table V*. Similar groups were sensitized with horse serum and with Bolton toxin. Administration of the antigen produced similar but more severe prostration than that produced by Compound 48/80. There were comparable but less severe effects in those treated with Bolton toxin; for example, in the groups treated with antigen the effects developed within 1–2 minutes after intravenous injection, but were delayed for 2–5 minutes and lasted for 10–15 minutes only following the administration of Bolton toxin. *Table V* lists the reduction in histamine values in each case. The antigen–antibody reaction produced considerable fall in the histamine content of various tissues; after injection of Bolton toxin there was a small reduction in tissue histamine comparable to that elicited by Compound 48/80 in this species.

The effects of Compound 48/80 on the gastric mucosa were those of erosion and ulceration. Erosions were occasionally produced by single intraperitoneal injections (4 mg./kg.) of Compound 48/80 (*Fig.* 197 B), but the effects were greatly intensified by pre-treatment with aminoguanidine (*Fig.* 197 C) and the histamine values were augmented in plasma samples examined (*Table I*, B). *Fig.* 197 D, E, F illustrates the appearance of the stomach after anaphylactic shock, after Bolton toxin, and Bolton toxin plus aminoguanidine. In each case there is marked engorgement of the gastric mucosa and the effects have been intensified by the antihistaminase agent, which suggests that local release of histamine plays a part in their production. Conversely, the effects were diminished, or were absent, after prior treatment with Compound 48/80, and the appearances were substantially the same as in *Fig.* 197 A.

DISCUSSION

On injection of Compound 48/80 and horse serum into rats there was a fair degree of histamine release into the blood-stream, one sequel of which was the occurrence of gastric ulceration. These effects were intensified by aminoguanidine, which is an agent which prevents the enzymatic destruction of histamine. In contrast, Compound 48/80, which is an agent which releases tissue-histamine stores, could be used to deplete the tissue-histamine stores slowly with minimal toxic effects; subsequent challenging with horse serum was then ineffective. It should be noted that horse serum in rats acts as a primary histamine liberator, that is to say, it can act without prior sensitization of the animal. Gastric ulceration may then be induced by horse serum acting like any other histamine liberator, without the need for sensitization by local administration directly into the stomach wall followed by later injection of antigen systemically at a later date, as described by Jahiel, Jahiel, and Krakauer (1952) for rabbits.

In guinea-pigs the effect on the histamine of skin and skeletal muscles is, by comparison with rats, not at all striking, but this may be the result of the fact that the local store of histamine in this species is not high at this site. In this species it is well known that the tissues of the lung and gastro-intestinal tract contain the greatest concentrations of histamine. Nevertheless, there was little release of histamine on arterial perfusion of the viscera with Compound 48/80; furthermore, after continuous treatment with it there was still a comparatively small effect on the histamine at these sites. It may be that there is a limiting factor to release of larger quantities of tissue histamine, provided to offset the susceptibility of this species to histamine itself. It was estimated for instance by Mayer (quoted by Dubos, 1952) that the guinea-pig is at least 700 times more sensitive to histamine than the rat.

Attempts were made to minimize the reaction to the release of histamine by injecting large volumes of Compound 48/80 in dilute concentration, by injecting it in a retard medium, and by injecting mepyramine to antagonize the released histamine. The greatest reduction in tissue histamine occurred when Compound 48/80 and mepyramine were administered together. A possible explanation lies in the fact that the antihistamine, mepyramine, is paradoxically a strong histamine-releasing agent (Arunlakshana, 1953) and the two substances may together exert an enhanced effect.

Guinea-pigs treated with Compound 48/80, though showing the slightest evidence only of reduction of histamine in the tissues, showed typical histamine effects, as did others sensitized with horse serum after administration of the antigen; similar effects were produced by gastrotoxin or Bolton toxin. The effects of gastrotoxin were furthermore aggravated by the use of aminoguanidine which prevents destruction of histamine by histaminase. Such a result strengthens the belief that gastrotoxin exerts its effects via the intermediary agency of histamine.

This was again proved likely by preliminary slow release of the labile histamine of the tissues with small doses of Compound 48/80 administered some time before the injections of gastrotoxin. Under these conditions gastrotoxin could be rendered ineffective. It is concluded that the specific gastrotoxin described by Bolton exerts its effects as a histamine liberator.

SUMMARY

1. Intravenous and intraperitoneal injections of Compound 48/80 in guinea-pigs and rats cause gastric erosions and ulceration which are the result of histamine release.

2. Prolonged treatment with Compound 48/80 effected considerable reduction in the tissue histamine of rats. The reduction of tissue histamine of guinea-pigs was by comparison slight; more thorough release of histamine was prevented by the outstanding sensitivity of guinea-pigs to small amounts of released histamine. Measures to antagonize or counteract the intensity of the histamine-like effects were adopted, but these in turn influenced the process of histamine release. In the case of mepyramine, the histamine liberation from the tissues was even accentuated.

3. Horse serum produces the same effects as a histamine liberator in rats; the gastric effects are intensified with the antihistaminase, aminoguanidine. The effect of horse serum is invalidated by prior histamine release effected by small doses of Compound 48/80 given over a prolonged period.

4. Release of histamine accounts for the action of gastrotoxin or Bolton toxin in guinea-pigs. Comparable effects on the stomach are produced by Compound 48/80 and anaphylactic shock. Aminoguanidine acting as an antihistaminase intensifies these effects. Prior treatment with Compound 48/80 in small doses over a prolonged period invalidates the effects of gastrotoxin given subsequently.

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THE INFLUENCE OF THE SECRETORY FUNCTION OF THE STOMACH ON NUTRITION IN THE DOG

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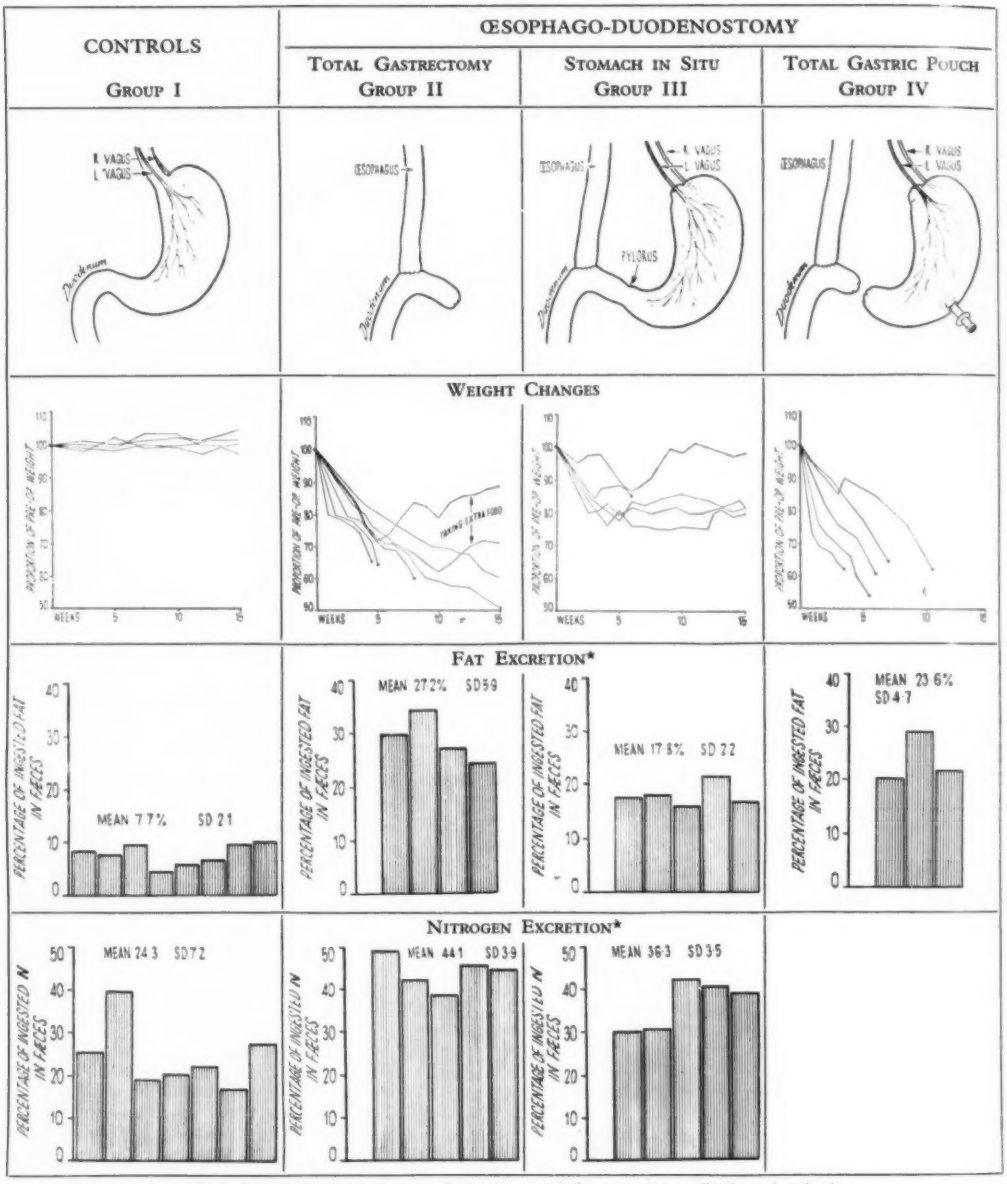
"*. . . of the stomach . . . it is only to be considered as a gland with a cavity*".—JOHN HUNTER.

THE nutritional disturbances which may follow gastric resection in man are well known and have been investigated intensively. Their underlying causes, however, are not completely understood and, until they are, it is unlikely that the deficiency syndromes will be prevented or treated adequately. In a previous experiment in the rat we found that the secretory function of the stomach was more important than its reservoir function in the maintenance of body-weight and hæmoglobin concentration (Welbourn and Doggart, 1956); the absorption of fat, however, was improved by the loss of the secretory portion of the stomach, while in man and the dog it is impaired by gastrectomy (Glazebrook and Welbourn, 1952; Welbourn, Hallenbeck, and Bollman, 1953). Since the efficiency of the intestinal absorption of food is probably a factor which influences the nutritional state after operation, it is clearly impossible to apply to man the results of this experiment on the rat. The alimentary tract of the dog is more like that of man and it was therefore chosen for this study.



* Each column represents the mean between one and five excretion studies in each animal.

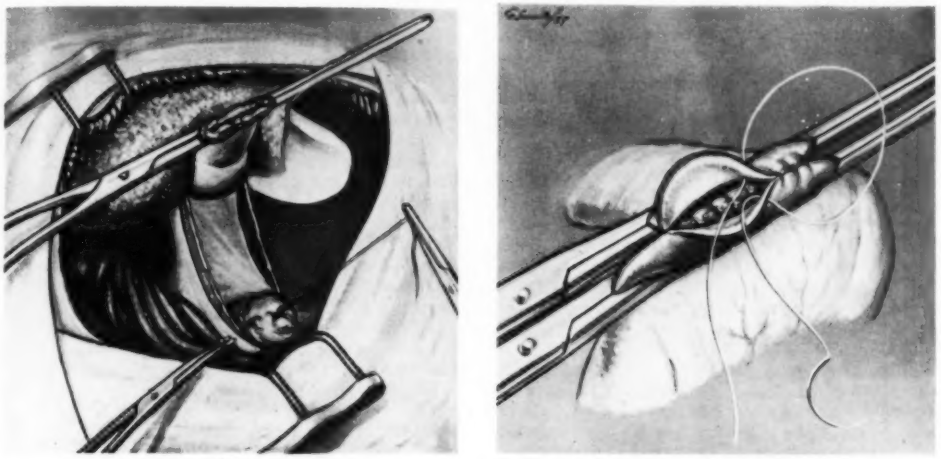
FIG. 198.—Preparations used and summary of data (body-weight and fat and nitrogen excretion).

Little is known about the relative importance of the secretory and storage functions of the stomach in the maintenance of nutrition in man and in the dog. The evidence, which is conflicting, comes from four sources:—

1. The operation of by-passing the stomach by means of a loop of small intestine in cases of benign œsophageal stricture leaves the stomach as a secretory organ but eliminates it as a reservoir. There are contradictory reports about the effects of this procedure on nutrition. Yudin (1944), who has performed the operation many times in children, claims that there is no disturbance of metabolism, hæmopoiesis, or growth. Gross (1953), on the other hand,

condemns the operation because in his experience it restricts growth. Brain (1953) has also found that the nutritional state of patients suffers after operation.

2. Several different methods have been devised recently for the provision of a new reservoir for food after gastrectomy. All employ loops of jejunum



A B C

FIG. 199.—Operative technique. A, The œsophagus has been divided and the distal end closed. Both vagal nerves are intact. B, The end-to-side œsophago-duodenal anastomosis. C, The stomach has been exposed through an abdominal incision in order to insert the cannula.

or colon for the construction of a false 'stomach'. There is no clear evidence that the nutritional state of patients or of dogs is improved by these operations (Everson, 1952; Johnson, Goldman, Davis, McCorkle, Harper, and Gardner, 1952; Kelly and Wangensteen, 1954; Free, Mannix, and Beal, 1956; Robinson and Pittman, 1957).

3. Vagotomy performed either alone or in combination with gastro-enterostomy or pyloroplasty reduces the gastric secretions but leaves a normal sized, though flaccid, reservoir. Nutrition is impaired less by these operations than by gastrectomy (Johnson, 1948; Davies, 1956; Shingleton and Baylin, 1956).

4. Loss of weight after gastrectomy in the dog is said to be reduced if a small portion of stomach is either left as a cuff at the lower end of the œsophagus or inserted as a patch on the efferent jejunal loop (Amann and Brunschwig, 1956). The data, however, are not presented in a convincing manner.

Our purpose in this experiment was to observe the effects of the gastric secretion on nutrition. We did this by eliminating the stomach as a reservoir, while retaining it as an organ of internal or external secretion. Observations were made on body-weight, the hæmoglobin and plasma protein concentrations, and on the excretion of fat and nitrogen in the fæces.

METHODS

Thirty-eight mongrel dogs of both sexes were used, 20 of which were available for study. Their pre-operative weights varied from 8 to 15 kg.

Four different groups were prepared (*Fig.* 198):—

Group I.—Normal controls.

Group II.—Œsophago-duodenostomy with total gastrectomy.

Group III.—Œsophago-duodenostomy with the stomach in situ. The stomach was excluded as a reservoir, but retained as an organ of secretion. The external secretion flowed into the duodenum.

Group IV.—Œsophago-duodenostomy with a total gastric pouch. This was the same as Group III, except that the external secretion was drained to the exterior. Any internal secretion could still enter the circulation.

OPERATIVE TECHNIQUE

(*Fig.* 199)

The dogs were anæsthetized with ether. An endotracheal tube was passed and respiration was controlled. The operations were done transthoracically through the left tenth intercostal space. The

diaphragm was divided from the middle of the tendinous portion to the gastro-œsophageal junction and the lower end of the œsophagus was mobilized and divided. In the dogs in which the stomach was preserved the vagus nerves were dissected and left intact and the cardiac end of the stomach was closed and invaginated (*Fig.* 199 A). An end-to-side œsophago-duodenal anastomosis was done in two layers

Table I.—Causes of Immediate Post-operative Deaths

Cause of Death	Number of Deaths
Post-operative shock	1
Leaking œsophago-duodenal anastomosis and peritonitis	4
Empyema and lung abscess	4
Strangulation of small bowel after herniation through new hiatus	4
Gangrene of lower œsophagus	2
Asphyxiation with regurgitated food	1
Unexplained	2
Total	18

with inner interrupted and outer continuous sutures of linen thread (*Fig.* 199 B). The total gastric pouch was drained by means of a cannula, stitched into the stomach (*Fig.* 199 C). The secretions were collected in a rubber bag, which was attached to the cannula and held in position by a cloth coat. The secretions were emptied from the bag daily and their volume and hydrochloric acid content were measured. Additional salt was given to these animals to compensate for that which was lost.

Eighteen dogs died as a direct result of operation (*Table I*).

EXPERIMENTAL PROCEDURES

The dogs were fed once daily with a measured quantity of standard laboratory diet (*Table II*), sufficient to provide approximately 70 calories per

Table II.—Details of Diets

	Standard Diet g.	High Fat Diet g.
Composition (per 100 g.)		
Beef offal	21	17
Pork offal	14	12
Gravy	15	12
Pig starter meal	50	42
Lard		17
Total	100	100
Analysis (per 100 g.)		
Protein	16·5	13·7
Fat	3·5	19·9
Carbohydrate	23·5	19·7
Calories	200	255

kilogram of pre-operative body-weight. This amount of food maintains healthy dogs at a constant weight in this laboratory (*Fig.* 198). The animals were weighed twice weekly.

The excretion of fat and nitrogen was measured by means of intake and output studies in which the animals were placed in metabolism cages and fed on a high fat diet (*Table II*) for six days. On the first two and on the sixth days the diet was uncoloured. From the third to the fifth days a known weight of the diet, coloured with 0·2 per cent of carmine, was given. The amount of coloured food which was left uneaten was measured, and all the coloured fæces were collected and preserved in dilute hydrochloric acid. The fæces were mixed with water and emulsified in an electric homogenizer. When, as sometimes happened, diarrhœa caused contamination of fæces with urine, estimations of nitrogen were not made. This happened so frequently in dogs with total gastric pouches that no adequate data about nitrogen excretion are available in this group. The fat content of the diet was estimated in each batch by an ether extraction method and that of the fæces by the wet extraction method of Van de Kamer, Huinink, and Wyers (1949). The nitrogen was measured by Kjeldahl digestion and titration. The 'macro' method was used for the diet and the 'micro' method for fæces.

The hæmoglobin and plasma protein concentrations were estimated monthly. Hæmoglobin was measured with a grey-wedge photometer and the proteins by the Kingsley modification of the Biuret method (Kingsley, 1940).

Radiographic examination of the alimentary tract was made while the animals were fed with a mixture of food and barium sulphate suspension. The dogs were fed in the standing position and screened from the left side.

RESULTS

1. Body-weight.—All the dogs lost weight after operation. Those in which the gastric juice entered the duodenum (Group III—œsophago-duodenostomy

Table III.—Weight of Food eaten by Different Groups during Test Periods

Group	Number in Group	Total Observations	Average Weight of Food eaten (g. per kg. of Pre-operative Body-weight per Day)	S.D.
Control I	8	8	27·8	1·7
II	4	9	29·8	6·6
III	5	18	23·8	6·4
IV	3	4	11·0	5·0

Statistical Analysis.—Comparing Groups II and III, t (7 D.F.) = 1·3. $0{\cdot}4 > P > 0{\cdot}3$.

with stomach in situ) lost much less weight than those which had undergone other operations (Groups II and IV) (*Fig.* 198). Every dog in Group III remained at 75 per cent or more of its pre-operative weight, while all those in Groups II and IV fell below this level. Loss of weight was most rapid in the first three to four weeks after operation. Four out of seven without stomachs and all those with total gastric pouches became so emaciated that they had to be killed for humane reasons. Two dogs with their stomachs in situ died from acute gastric dilatation many weeks after operation.

2. Food Intake.—The dogs ate little food immediately after operation, and vomited frequently. After about one month most of the dogs usually ate all the food that was offered. Unlike normal dogs they did not bolt it, but ate it slowly throughout the day. The exact amount that was eaten was calculated during the intake and output studies. The mean intake in Groups I, II, and III was about the same (*Table III*). If anything, those which had undergone total gastrectomy tended to eat more than the others. Those in Group IV ate appreciably less.

All the animals whose weights fell to two-thirds of the pre-operative level (i.e., all in Groups II and IV) were offered 50 per cent more food. Two animals only (Group II—total gastrectomy) accepted it and put on weight (*Fig.* 198).

During the last few weeks of life, when their nutritional state was poor, the dogs ate progressively less.

Table IV.—Statistical Analyses of Data in Fig. 198

Compared Groups	Degrees of Freedom	Difference between Means	t	P
Fat Excretion				
I and III	11	11·6	9·6	0·001 > P
III and II	7	9·4	3·3	0·02 > P > 0·01
III and IV	6	5·8	2·4	0·05 > P > 0·02
II and IV	5	3·6	1·3	0·3 > P > 0·2
Nitrogen Excretion				
III and I	10	12	3·4	0·01 > P > 0·001
III and II	8	7·8	2·5	0·05 > P > 0·02

Table V.—Plasma Protein and Hæmoglobin Concentrations in Dogs which survived Five Months or Longer after Operation

Group	Time after Operation (months)	Total Plasma Proteins (g./100 ml.)	Hæmoglobin Concentration (g./100 ml.)
I Normal (mean of 8 dogs)	—	6·8 (S.D. = 0·6)	14·9 (S.D. = 0·5)
II Total gastrectomy 1	6	5·5	11·1
	8	4·4	9·3
	11	4·3	7·8
II 2	5	5·3	7·8
	7	5·8	
II 3	6	5·4	13·3
	8	5·7	14·8
III Œsophago-duodenostomy with stomach in situ 1	5	4·9	8·9
	6	4·6	
III 2	6	5·8	12·9
	8	5·2	12·3
	9	5·3	11·2

3. Excretion of Fat and Nitrogen.—All the animals which had had operations excreted more fat and nitrogen in the fæces than the controls. Excretion was greatest in those which had undergone total gastrectomy (Group II), and least in those whose gastric secretions flowed into the duodenum (Group III). Dogs with total gastric pouches excreted similar amounts of fat to those without stomachs (*Fig.* 198 and *Table IV*).

4. Hæmoglobin Concentration.—All the dogs which survived five months or more after operation developed an anæmia of the microcytic hypochromic type. The degree of anæmia was not influenced by the type of operation (*Table V*).

Table VI.—Average Volume and Composition of Secretions from Total Gastric Pouches—Group IV

Volume per dog per day	300 ml.
*p*H	1·3
Sodium ions	69·5 m. Eq./l.
Chloride ions	270 m. Eq./l.

5. Plasma Proteins.—The plasma protein concentration fell similarly in all the animals which survived five months or longer (*Table V*).

6. Radiographic Studies.—Barium meals in the dogs in Group III (œsophago-duodenostomy with stomach in situ) showed that food was swallowed normally. After it had entered the duodenum, however, the greater part of each bolus was regurgitated into the œsophagus. Often it entered the mouth and was either swallowed again or vomited. A to-and-fro movement across the œsophago-duodenal anastomosis was usually observed for five to ten minutes before the bolus eventually passed on. In no case was there any sign of retrograde passage of food into the stomach. The appearances were exactly similar in dogs which had undergone total gastrectomy. In both groups the passage of food through the duodenum and upper jejunal loops was very rapid, but there was usually a compensatory delay in passage through the ileum.

7. Analysis of Juice from Gastric Pouches.—The volume of the gastric juice, which was collected from the dogs with total gastric pouches (Group IV), averaged 300 ml. per day. Since the gastric phase of secretion is eliminated, this is probably appreciably less than that produced by the intact stomach. The composition, however, was similar (*Table VI*).

DISCUSSION

The radiographic studies show that the stomach is in fact eliminated as a reservoir in the preparations in which it is not removed (Groups III and IV). Analysis of the juice from the total gastric pouches (Group IV) shows that the stomach is retained as an organ of secretion, but that the volume secreted is probably less than normal.

There are three possible immediate causes of loss of weight after removal of the stomach, namely: (1) Reduced consumption of food; (2) Increased excretion of food derivatives in the fæces; and (3) Increased utilization of food in the body.

1. The consumption of food may be considered at two distinct periods after gastrectomy. In the first, which follows immediately after operation, the dogs eat little food and lose weight rapidly. In the second, food consumption increases and, by eating slowly, the dogs are able to take amounts which are

adequate to maintain healthy animals in a state of normal nutrition. Weight, however, continues to fall, though less rapidly than before. A few dogs are able to eat *more* than this amount of food and to regain weight which they have lost. This indicates that a reduced intake of food alone does not account for the loss of weight and that an increased intake may be able to compensate for the other cause or causes of weight-loss. Ivy (1940) confirms that a dog after gastrectomy requires 25–50 per cent more food than normal to maintain its weight.

2. A greatly increased excretion of fat and nitrogen in the fæces is found constantly after total gastrectomy. It can be seen from the calculation in *Table VII* that the loss which this represents is probably sufficient to account for the loss of weight during the period when the animals are eating normal quantities of food. This calculation involves two assumptions. The first is that a weight of body fat, equivalent to that lost in the fæces, is metabolized for the provision of energy and is thereby lost. This assumption is probably correct. The second, for which we have no direct evidence, is that the nitrogen lost in the fæces represents protein lost from the body.

3. The rate at which food is utilized in the body can be estimated by measuring the basal metabolic rate. We have no knowledge of any such observations in the dog or in man after removal of the stomach, but we have found no increase in oxygen consumption after gastrectomy in the rat (Johnson and Welbourn, to be published).

The main purpose of this experiment was to investigate the more *remote* causes of loss of weight after removal of the stomach and to discover how the immediate factors, which we have just been discussing, are influenced by the reservoir and the secretory functions of the stomach respectively.

It is clear that dogs whose gastric secretions enter the duodenum, but which have no gastric reservoir (Group III), maintain weight better than those whose stomachs have been removed (Group II). This indicates that the gastric juice plays a part in preserving body-weight.* It probably does so by aiding the absorption of food, since the amount consumed by the two groups is the same, while the amount excreted is less in the animals whose gastric secretions flow into the duodenum. The calorific value of the food derivatives excreted in the fæces in the latter group is at least enough to account for their loss of weight (*Table VII*). Dogs whose secretions are drained to the exterior (Group IV) lose weight and excrete food derivatives in the fæces in a similar way to those which have had their stomachs removed, indicating that there is probably no *internal* gastric secretion concerned with the maintenance of body-weight.

The gastric juice may influence the absorption of food by stimulating the external secretion of the pancreas. Annis and Hallenbeck (1952) found that pancreatic secretion was reduced by partial gastrectomy but could be restored by the introduction of hydrochloric acid into the duodenum. More recently it has been found, with a radio-active technique, that the absorption of fat after partial gastrectomy in man is increased by the feeding of pancreatic extract mixed with food (Shingleton, Isley, Floyd, Sanders, Baylin, Postelthwaite, and Ruffin, 1957). We have been unable to confirm this observation by our technique either in dogs without stomachs (Group II) or in those with their stomachs by-passed (Group III).

Table VII.—Calculation of Relation of Loss of Food Derivatives in the Fæces to Loss of Weight while Dogs were eating Normal Quantities of Standard Diet*

	Normal Group I g.	Total Gastrectomy Group II g.	Œsophago-duodenostomy Group III g.
Fat.—			
Average loss of fat in fæces per dog per day	0·94	3·3	2·2
Average loss per day in excess of normal dogs		2·4	1·2
Weight of water associated with this weight of fat in body tissues†		0·4	0·3
Loss of body-weight per day from this source		2·8	1·5
Protein.—			
Average loss of nitrogen in fæces per dog per day	2·25	4·1	3·4
Average loss per day in excess of normal dogs		1·8	1·1
Weight of protein from which this weight of nitrogen is derived		11·4	6·9
Weight of water associated with this weight of protein in body tissues‡		8·6	5·2
Loss of body-weight per day from this source		20·0	12·1
Total Calculated loss of body-weight per day—fat plus protein		22·8	13·6
Average loss of body-weight per day actually observed (*Fig.* 198)		25·0	8·0

* It is assumed that the amounts of fat and nitrogen which are lost form a constant *proportion* of the amounts which are eaten irrespective of whether the diet is 'standard' or 'high fat'.

† Assuming that adipose tissue contains 20 per cent of water by weight (Best and Taylor, 1945).

‡ Assuming that muscle protein contains 75 per cent of water by weight (Best and Taylor, 1945).

The gastric reservoir appears to perform two functions. First, it allows the normal dog to eat its daily requirement of food within a few minutes. The dog whose œsophagus is joined to the duodenum cannot do this and is obliged to eat small quantities at intervals throughout the day. Secondly, it permits food which has been well prepared to enter the small intestine slowly. When food enters the duodenum from the œsophagus it passes very rapidly

* It is possible that the influence of vagotomy on the abdominal viscera contributes to the ill effects of total gastrectomy. However, vagotomy alone does not increase the excretion of fat (Welbourn, Hallenbeck, Bollman, 1953).

through the upper jejunum. This phenomenon is not influenced by the preservation of the gastric secretions and probably accounts entirely for the somewhat defective absorption of food in animals whose stomachs have been by-passed.

The anæmia which is found in all the dogs which survived several months after operation is not influenced by the presence of the gastric secretions and is therefore probably caused by intestinal hurry.

We may conclude that in the dog the external secretory function of the stomach is important in the maintenance of body-weight and in the prevention of abnormal losses of food derivatives in the fæces. The reservoir function, however, is also necessary for the preservation of a normal state of nutrition.

SUMMARY

1. An experiment was devised to discover the relative importance of the secretory and reservoir functions of the stomach in the maintenance of nutrition in the dog.

2. Four groups of animals were used: I, Controls; II, Total gastrectomy; III, Œsophago-duodenostomy with stomach in situ; and IV, Total gastric pouch.

3. The dogs in which the gastric juices flowed into the duodenum lost less weight and excreted less fat and nitrogen in their fæces than dogs in any other group.

4. Anæmia and hypoproteinæmia developed similarly after each type of operation.

5. The intake of food was unaltered by the operations.

6. It is concluded that the gastric secretions influence nutrition in the dog by aiding the intestinal absorption of food.

7. There is *no* evidence that the stomach elaborates an *internal* secretion which influences nutrition in the dog.

Acknowledgements.—We are grateful to Mr. D. W. Neill, Principal Scientific Officer, Biochemical Laboratory, Royal Victoria Hospital, and to Mr. R. H. Thompson of the same laboratory for the plasma protein estimations; Dr. M. G. Nelson, Clinical Pathologist, Royal Victoria Hospital, for the use of the hæmoglobinometer; Mr. G. A. Smith for the diagrams and illustrations; Mr. R. G. Wood and Miss E. Scott for the photographs; and Mrs. P. Kemp for the typing.

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EXPERIMENTAL BONE LENGTHENING BY EPIPHYSIAL DISTRACTION

By P. A. RING

FROM THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

THE treatment of limb inequalities by lengthening the shorter member has never gained wide acceptance, although a large series of successful bone elongations has been recorded by Allen (1948, 1951). The difficulties of the procedure lie partly in the stretching of soft tissues, a difficulty which is inherent in any method of rapid bone elongation, and partly in the problem of maintaining the alinement of the fragments and in the production of firm bony union. Lengthening of leg bones has most commonly been performed in the tibial shaft, a region which is notoriously prone to delayed union and to non-union. The average time before weight-bearing was permitted in Allen's series was 6½ months, but delay of up to a year was not uncommon. Lengthening of the femur was completed in a shorter time (5 months), although the gain in length was not quite so great as in the tibia. Best and Larsen (1956), using an intramedullary rod to control the alinement of the femoral fragments, found that the average period before union occurred was considerably longer.

In the course of other experiments upon the epiphysial cartilage it was noted that there was a natural plane of cleavage in the centre of the cartilage

columns. If lengthening of a bone could be produced in the centre of this osteogenic area it might be expected to promote rapid new bone formation, without giving rise to the problems of control of small bone fragments. In the present study an attempt has been made to examine the practical problems of bone lengthening in this region in the experimental animal.

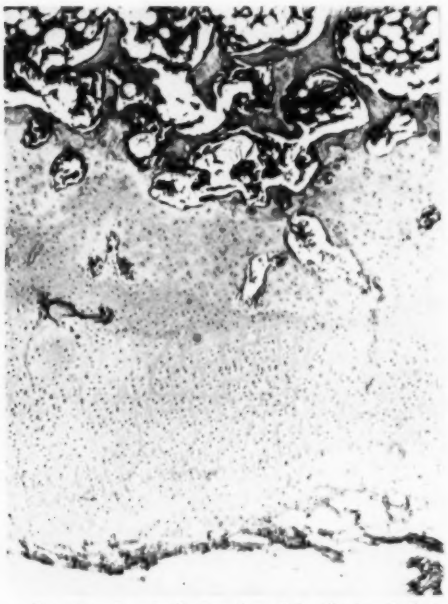

FIG. 200.—Longitudinal section of the distal end of the radius showing the plane of separation passing through the base of the cartilage columns. (× 48.)

METHOD

Twenty mongrel puppies between 4 and 6 months of age were anæsthetized with intraperitoneal nembutal, and the distal end of the right forelimb was exposed. A short length of Kirschner wire was driven through the lower bony epiphyses of the radius and ulna. A second wire, parallel with the first, and about 2 inches proximal to it, was passed through the shafts of these bones and the wounds were then closed. The ends of the wires were united by short turnbuckles, and the forelimbs were radiographed by a standard technique to permit comparable measurements to be obtained of the lengths of each forelimb.

Table I.—LENGTHENING OF RADIUS IN ANIMALS SURVIVING UNTIL MATURITY

DOG No.	PERIOD OF STUDY (weeks)	INITIAL GAIN mm.	FINAL GAIN mm.	OBSERVATIONS
3	10	11	6	1. Fracture of lengthened bone 2. Premature epiphysial fusion
5	13	14	7	Premature epiphysial fusion
6	5	23	7	Fracture of lengthened bone
7	8	22	12	Fibrous union only
8	9	23	13	Delayed union
9	15	21	4	Fracture of lengthened bone
10	15	25	15	Premature epiphysial fusion
11	13	28	5	Fracture of lengthened bone
19	12	16	9	—
20	12	32	14	Fracture of lengthened bone

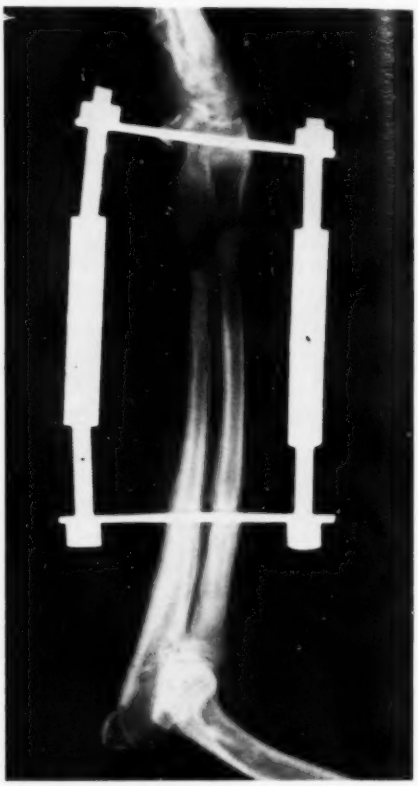

FIG. 201.—Radius and ulna with pins and turnbuckle in position showing new bone formation by the periosteum two weeks after distraction had begun.

The right leg was then enclosed in plaster covering the turnbuckles, and the plaster was subsequently split transversely, midway between the two wires.

A gradual displacement of the epiphyses of the radius and ulna was achieved by rotating each turnbuckle once daily, the thread permitting an increase in length of 10 mm. a week. The separation was confirmed by radiographs at weekly intervals. At the end of four weeks the plaster was removed to permit the stability of the lengthened bones to be estimated, and to allow further standard radiographs of bone length. The leg was once again immobilized, either with or without pins in position, until the lengthened bone appeared to be clinically and radiologically sound.

OBSERVATIONS

Of the 20 animals subjected to this procedure 5 died of intercurrent disease and the bones were

sectioned, and 5 others were specially sacrificed to provide material for histological study. The remaining 10 animals survived until serial radiographs demonstrated that the control limb was no longer growing; 8 of them showed bony consolidation of the lengthened limb, 1 showed an unstable fibrous union only, and 1 was killed immediately after a fracture through the lengthened bones. In *Table I* the gain in length at the end of the period of distraction, and gain in length recorded at biopsy, and the complications of the procedure in each animal are briefly recorded. For convenience only the changes in the radius are recorded, those in the ulna being identical.

FIG. 202.—Radiograph of the radius and ulna shortly after distraction had been completed, showing filling-in of the metaphysial region and a relatively normal epiphysial cartilage.

No difficulty was experienced during the period of epiphysial distraction with the maintenance of alinement of the limb, and the actual lengthening caused no discomfort. At the end of the month of distraction the limb appeared to be clinically solid in 3 animals; in the 7 others a variable amount of movement was detectable. Failure to immobilize the limb in plaster invariably led to a fracture through the lengthened bone with ventral displacement of the distal fragments. Although the fractures appeared to unite readily, much of the gain in length was lost. A period of about 4 weeks after lengthening had been concluded appeared to be necessary for complete consolidation of the newly formed bone; one animal required five weeks, and another killed after four weeks showed radiological and histological evidence of fibrous union only.

FIG. 203.—Fracture through the lengthened bones following premature removal of plaster. On the dorsal aspect of the radius the spike of periosteal bone formation is visible and the small amount of new bone formed by the epiphysial cartilage can also be seen.

The distraction of the epiphysis produced a line of separation between the calcified and non-calcified parts of the cartilage columns, and the gap between these two elements filled with blood-clot which was limited laterally by the intact periosteum (*Fig.* 200). New bone was first laid down by the osteoblasts of the periosteum, and a cylinder of bone was formed encircling the region of bone lengthening (*Fig.* 201). This cylinder was often incomplete proximally, and the gap in this region contained a number of osteoclasts, and closely resembled the area of remodelling of the normal metaphysis. This was the area of weakness through which subsequent fractures were prone to occur. The epiphysial cartilage and the metaphysis, separated by the blood-clot, each produced a limited amount of new bone, which contributed to the central consolidation. The histological structure of the epiphysial cartilage in

most specimens during the period of lengthening was essentially normal, although in one animal there was extensive fibrous replacement, which was probably the precursor of epiphysial fusion.

At the conclusion of the phase of distraction the periosteal cylinder was usually well formed, and in some animals a central mass of bone was also present, emphasizing that the loss of bone continuity during this procedure was minimal. During the next two weeks the metaphysis became consolidated (*Fig.* 202). In the radiographs a dense band of new bone indicated the site of elongation, whilst the sections showed that the epiphysial cartilage and the surrounding bone were almost normal. By the end of the fourth week after lengthening had ceased it was possible to determine the subsequent fate of the limb. In 5 animals the lengthened bone had sustained a fracture, necessitating a further period of immobilization (*Fig.* 203). Three animals showed evidence of premature fusions of the radius. In 5 animals the radiological picture had reverted to normal, and subsequent radiographs showed that the epiphysial cartilage was still active and that relative lengthening of the bone was maintained until growth had ceased (*Fig.* 204).

FIG. 204.—A radiograph of the radius and ulna showing the normal appearance of the growing end of the bone eight weeks after distraction had been completed.

The gain in length at the end of four weeks' distraction rarely equalled the expected gain. This was partly due to bending of the wires in the early experiments—a 2-mm. wire is necessary to prevent this complication—but mainly due to the growth of the control limb. The final gain in length was always less than predicted, partly because of collapse of the bones after fracture, partly due to premature epiphysial fusion, and partly due to the restraint of growth by immobilization with the wires in situ until consolidation was complete. Nevertheless, each of the treated forelimbs was longer than the control, and the gain in length was often considerable (*Fig.* 205). Premature fusion of the epiphyses was not a significant cause of loss of length, mainly because the animals affected were nearing maturity.

FIG. 205.—The dried bones at the conclusion of the experiment.

DISCUSSION

In view of the way in which increasing pressures across the epiphysial cartilage retard the growth of bone (Haas, 1948; Blount and Zeier, 1952) it is tempting to regard the present method of bone elongation as depending, at least in part, upon the reduction of tension within this area. Such experimental evidence as there is, however (Gelbke, 1951), suggests that traction alone has no influence upon the rate of growth of bone, and it is probably better to regard this method of lengthening as completely dependent upon the production of epiphysial separation. The main source of new bone is then the undivided periosteum, and provided the rate

of distraction is not too great, it is possible to maintain bony continuity from this source alone. In the consolidation of the region of lengthening the metaphysis and, to a lesser extent, the epiphysial cartilage appear to play a part.

From the experimental evidence which has been presented it is clear that the separation of the epiphysis is not necessarily followed by a disturbance of its function. There is a good deal of clinical evidence to support this view. The maintenance of growth appears to depend upon the integrity of the reserve zone of the epiphysial cartilage. This region is unaffected by separation provided it occurs, as it usually does, at the metaphysial end of the cartilage columns. Even if the plane of separation passes into the reserve zone, growth may be unimpaired, since Ford and Key (1956) have shown that central destruction is not incompatible with normal growth. Provided, therefore, that the periphery of the epiphysial plate is undisturbed, normal growth should be resumed at the end of this period of distraction, and this has certainly occurred in some of the animals which have been permitted to survive for long periods. Should epiphysial fusion occur, the gain in length in a young animal might well be lost or even reversed; that this has not occurred in the present series was largely due to the age at which the operation was performed.

The major practical problem encountered was a retardation of consolidation of the lengthened bone, and this resulted in fractures through the lengthened bone, delay in union, or non-union. Fractures through the lengthened bone were largely due to the increase of tension in soft tissues, and could have been avoided by a more meticulous immobilization until consolidation was complete. The one case of non-union in this series represented the only failure to produce true elongation of bone. This animal showed no evidence of osteogenic activity of the periosteum at any time, neither did the control limb grow during the period of study. It is possible that a generalized disturbance of growth contributed to this failure.

SUMMARY

A method of bone lengthening by epiphysial distraction has been described. The method depends upon the production of a traumatic epiphysial separation, which is followed by the deposition of new bone in the region of the metaphysis. In the puppy, gains in length have varied between 4 mm. and 15 mm.

The method has presented the following complications:—

1. Premature epiphysial fusion.
2. Non-union at the site of lengthening.
3. Fractures through the lengthened bone.

After the period of distraction, the epiphysial cartilage may revert to a normal histological and radiological appearance, and growth may proceed in the usual manner.

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SHORT NOTES OF RARE OR OBSCURE CASES

A CASE OF NEONATAL FIBROSARCOMA OF LUNG

BY DOUGLAS ROBB

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A MALE child of 8 lb. 5 oz., the first child of a mother of 29 years, was found to have its heart-beat in the right chest, and dullness over the left hemithorax. Radiologically the left chest was opaque and the heart displaced to the right (*Fig.* 206). Barium swallow showed the cardia and stomach to lie below a normally placed left diaphragm, thus suggesting that the mass was of thoracic origin.

On the second day of life a left thoracotomy displayed a yellowish-white spherical tumour occupying most of the lower lobe of the lung, with fringes of lung tissue around. No adhesions of pleural layers had taken place, there was no fluid in the chest, the hilar structures were normal and not infiltrated, and showed no enlarged glands. Left lower lobectomy was performed; recovery was uneventful and progress subsequently was good, the latest report ten months after operation confirming this, clinically and radiologically.

Dr. Stephen Williams, pathologist, described the specimen as follows:—

"LEFT LOWER LOBE (Oct. 4, 1956).—A left lower lobe which is distended by a soft, yellowish fleshy tumour mass measuring 6·5 × 6·0 cm. The tumour is partly encapsulated and surrounded by a thin rim of atelectatic lung tissue, except at one point where the tumour reaches the pleural surface. The cut surface shows a uniform faintly lobulated appearance with numerous vascular markings. There is no evidence of cyst formation. The tumour is clearly separated by a width of 0·5 cm. from the line of excision at the hilum. (*Fig.* 207.)

"HISTOLOGY (*Figs.* 208–210).—Sections show the tumour to consist of poorly differentiated round and

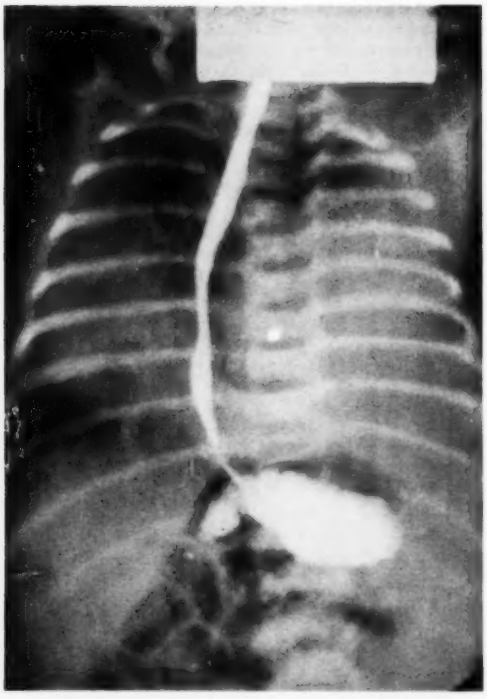

FIG. 206.—Pre-operative film showing mass in left chest displacing heart and œsophagus to right, with cardia and stomach normally below the diaphragm.

FIG. 207.—Photographs of specimen, pleural surface, and cut section.

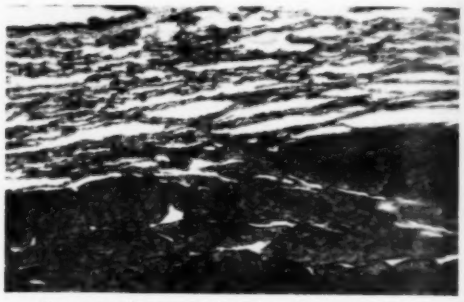

FIG. 208.—Microscopical section of tumour. (× 60.)

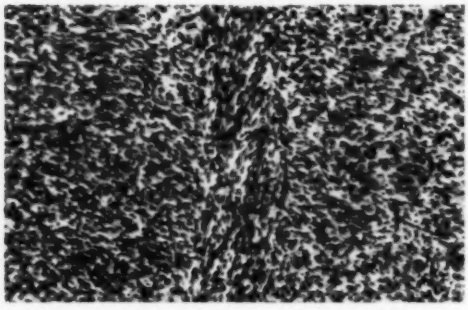

FIG. 209.—Microscopical section of tumour. (× 60.)

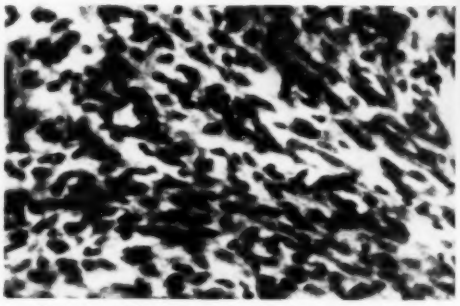

FIG. 210.—Microscopical section of tumour. (× 240.)

spindle cells arranged in sheets lying in various planes. Mitotic figures are present but are not numerous. The picture is that of a sarcoma, probably of fibroblastic origin. This view is supported by a Van Gieson stain which shows the production of collagenous fibrils in some areas. The peripheral lung tissue shows some degree of aeration: Fibrosarcoma of lung."

Alice Stewart and others (1956), writing from the Department of Social Medicine, University of Oxford, raise the question of intra-uterine irradiation as a cause of neonatal leukæmia and malignancy. In this case this seems inapplicable as the only X-ray exposure the mother had during pregnancy was one brief one to determine the lie of the fœtus two days before the baby was born, that is, four days before this large tumour was removed.

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CHYLOUS ASCITES IN INFANCY

By JOHN FAWCITT and H. M. GOLDBERG
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By the end of 1957 chylous ascites in the neonatal period had been reported 19 times. The literature was reviewed in 1951 by Gribitz and Kenof, who included 8 cases in infants in their series. Most cases have responded to a conservative régime of a low-fat diet and paracenteses when necessary. Surgical intervention has, therefore, rarely been indicated. Usually no lesion amenable to surgery has been discovered at laparotomy, but 3 cases of successful veno-peritoneal anastomosis have been reported (Whittlesey, Ingram, and Riker, 1955).

Frequent paracentesis with removal of large quantities of chyle is occasionally required. Dehydration and the loss of protein, fat, and fat-soluble vitamins may become a serious danger to life. It is, therefore, of interest to record a case where a lesion was found and dealt with at laparotomy, resulting in immediate cessation of the accumulation of chyle in the peritoneal cavity.

CASE REPORT

A full-term negro girl, weighing 8 lb., was born after normal labour on Nov. 2, 1957. The abdomen was prominent at birth and became more protuberant during the following days.

Meconium and urine were passed normally. Erect and supine radiographs of the infant were taken at the age of 10 days.

There was obvious evidence of ascites with only a small quantity of bowel gas. Both diaphragms were elevated but there was no evidence of hydrothorax. In the erect film the portion of bowel filled with gas floated upwards, and coils of it were seen beneath the right diaphragm (*Fig.* 211).

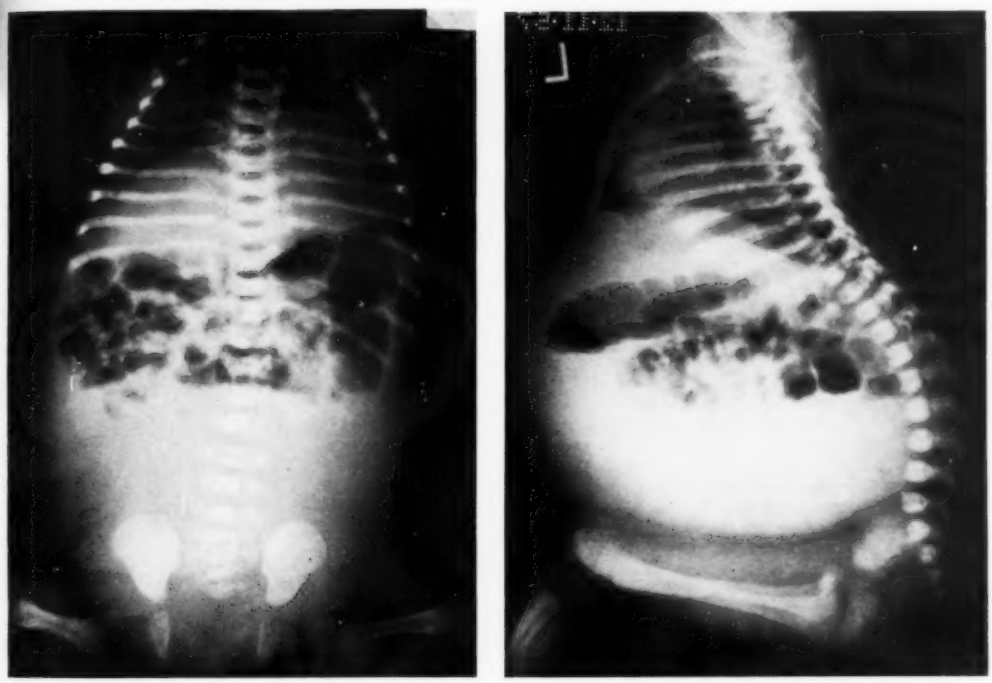

FIG. 211.—Radiographs showing portion of bowel filled with gas coiled beneath the right diaphragm.

On paracentesis 500 ml. of creamy looking fluid was withdrawn, but by the next day the abdomen was as distended as before. Further radiographs showed an increase in the quantity of gas in the bowel and coils of large and small intestine floating on fluid. In view of the biochemical hazards inherent in the frequent removal of large quantities of chyle, laparotomy was decided upon.

The abdomen was entered through a right paramedian incision; 700 ml. of chyle was aspirated from the peritoneal cavity. There was generalized congestion of the lacteals, and particularly those of the mesentery of the first loop of the jejunum. A smooth-edged defect 1 in. by ¼ in. in size was found at the root of this mesentery through which a constant flow of chyle was observed. This opening was closed by a continuous catgut suture, following which no further escape of chyle was seen.

The baby stood the procedure well, and at no time after the operation could any ascites be demonstrated.

Post-operative radiographs showed no significant quantity of intra-abdominal fluid.

Following this, gain in weight was satisfactory, but a low-fat diet was required to avoid diarrhœa and vomiting.

Laboratory examination of the ascitic fluid showed: Specific gravity, 1·015; fat, 0·6 g./100 ml.; protein, 3·2 g./100 ml.; chloride, 0·63 g./100 ml. (as NaCl); sugar, 72 mg./100 ml.; cholesterol, 105 mg./100 ml.

DISCUSSION AND CONCLUSIONS

We do not consider that the presence of chyle in the peritoneal cavity can specifically be recognized radiologically in the infant. The criteria put forward by Wyatt and Gross (1941) were not demonstrable in this case, nor were they seen in the cases reported by Chi-Hao Lee and Young (1953). It should be noted that the definitive liver shadow described by Wyatt and Gross was seen by them after operative intervention.

In cases where frequent tapping of large quantities of chyle leads to deterioration in health, laparotomy appears to be indicated. Even if no lesion is discovered in the peritoneal cavity which can be dealt with, veno-peritoneal anastomosis offers an alternative method of treatment.

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TUBERCULOSIS OF THE THYROID

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ALTHOUGH tuberculosis of the thyroid was recognized as long ago as 1847 (Albers, quoted by Nather, 1921), the first reference to the condition in the British literature was by Sir James Berry in 1890 when he was unable to find a specimen of the lesion in the museums of London, Oxford, Birmingham, Newcastle, Edinburgh, Glasgow, Geneva, Berne, or Zürich. Up to this time there had been much argument over the very existence of the disease, Rokitansky (1859) denying and Virchow (1864) accepting it, though believing it to be very rare. However, by the end of the nineteenth century it was a generally recognized disease, though the thyroid was believed to be resistant to tuberculosis—perhaps, as pointed out by Rankin and Graham (1932), accounting for the sending of patients with tuberculosis to areas of endemic goitre for treatment. Until Brüns (1893) first recognized the disease at operation, diagnosis was made histologically, and even now, except perhaps where overt tuberculosis is present elsewhere, the diagnosis is rarely made before operation except in a few cases of tuberculous abscess from which aspirated pus contains tubercle bacilli.

The disease may present in one of two ways: as an abscess, usually, but not always, associated with tuberculosis elsewhere; this mode of presentation has recently been reviewed extensively by Postlethwaite and Berg (1944); or as a nodule or tumour, unassociated with overt tuberculosis elsewhere. The lesions known as sclerosing thyroiditis and giant-cell thyroiditis previously thought to be tuberculous are not so considered now (Joll, 1952).

The case herein presented illustrates the second clinical type and corresponds closely with the only other case reported in the British literature by Keynes (1938), except in having no history of tuberculosis or of contact with it.

CASE REPORT

Mrs. Z. M., aged 21, of Cypriot origin, admitted in May, 1957, with a history of a swelling in the right side of the neck, of fairly rapid growth over two months to the size of a large hen's-egg. At the time of onset she thought she had had a 'cold' but otherwise was previously and subsequently perfectly well. She had no voice changes or symptoms referable to the respiratory, skeletal, or urinogenital systems.

General examination showed no clinical abnormality except for a fibro-adenoma in the right breast (proven histologically). Occupying clinically the entire right lobe of the thyroid was a mass, well defined, with a smooth surface, and remarkably hard for a thyroid 'adenoma'; it was considered to be an 'adenoma' into which hæmorrhage had occurred as radiography of the neck showed no calcification. There was no history or sign of pressure effect, no Horner's syndrome or paralysis of the vocal cords. A routine chest radiograph was considered to be normal. The patient was advised to have the 'tumour' explored with a view to its removal.

FIG. 212.—Operation specimen showing tuberculous area with several large caseous tubercles surrounded by a rim of normal thyroid tissue.

AT OPERATION (A. E. C., May 12, 1957).—Through a collar incision under general anæsthesia, the thyroid was explored. The isthmus and left lobe were in every way normal, but the greater part of the right lobe was occupied by a hard mass the size of a large hen's-egg and of the same shape; around the mass there was a rim of apparently normal thyroid tissue about ¼ in. thick. After mobilization of the periphery of the right lobe it was found that the deep aspect of the mass was adherent to the trachea and required to be cut off with the knife; at this stage a possibility of carcinoma was considered, but progress of dissection revealed a small caseous area and a diagnosis of tuberculosis was made. Subsequently the mass was removed *en bloc* by cutting through the rim of normal thyroid tissue to leave a strip posteriorly (*Fig.* 212). There was no erosion of the tracheal cartilages and after hæmostasis and dusting the wound with streptomycin (0·5 g.) the wound was closed without drainage. Uneventful healing occurred, but despite the observation previously that healing progresses satisfactorily without chemotherapy, a short course of streptomycin and P.A.S. was given as a caseous abscess had been entered.

In view of the intra-operative diagnosis of tuberculosis, extensive sputum, urinary, and radiological examinations were carried out without demonstrating any evidence of tuberculosis.

PATHOLOGY (Dr. Leslie Michaels).—"Around the periphery of the lesion are distorted thyroid acini, some of which contain colloid. Thyroid tissue has disappeared completely from the main bulk of the swelling which consists of a chronic inflammatory granuloma showing features strongly suggestive of tuberculosis. There are a number of early tubercles which are composed of epithelioid cells and an occasional Langhans giant cell which are surrounded by a zone of fibroblasts (*Figs.* 213, 214). These are common near the edge of the lesion, but nearer the centre they have fused together and have undergone extensive caseation. The caseous zones are infiltrated with polymorphs.

FIG. 213.—Photomicrograph from operation specimen. The presence of Langhans giant cells surrounded by fibroblasts is well seen. H. and E. (× 100.)

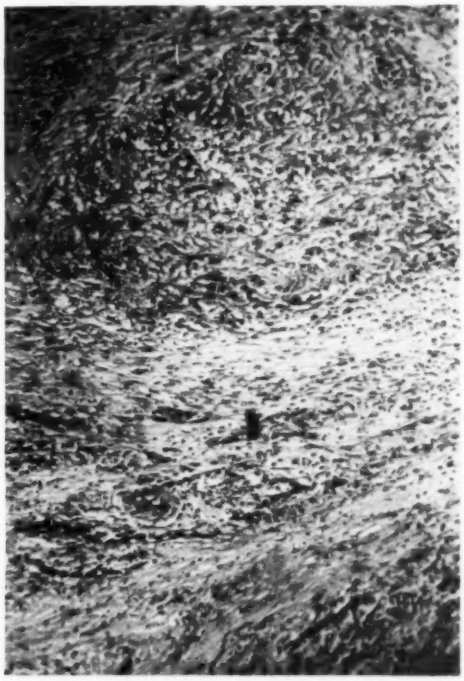

FIG. 214.—Illustrates the chronic inflammatory granuloma which occupies most of the operation specimen and has the characteristics of tuberculous caseation. H. and E. (× 100.)

"A careful search for tubercle bacilli in two Ziehl-Nielsen stained sections of the lesion has been unsuccessful, but failure to find the organisms in section is very common, even in cases where the diagnosis of tuberculosis is certain on other grounds. Thus, although the diagnosis of tuberculosis cannot be upheld with certainty, the histological appearances of a granulomatous lesion with caseation are so typical in this case as to make any other condition highly improbable."

COMMENT

As in the majority of cases reported in the literature, no suspicion of tuberculosis was entertained before exploration. Postlethwaite and Berg (1944) attempted to give a differential diagnosis of thyroid tubercle in order to make a pre-operative diagnosis, but as every thyroid swelling has to be included, the exclusion of non-tuberculous lesions becomes very difficult without recourse to histological or bacteriological examination. In view of the rarity of the lesion a therapeutic test course of antibiotics is out of the question in the ordinary management of thyroid swellings unassociated with overt tuberculosis elsewhere, and any hope of treating the lesion other than by surgery appears to be impracticable.

In the case presented no tubercle bacilli were demonstrable, but from the time when Nather (1921) first showed the bacillus in the thyroid and commented upon the difficulty of so doing, the inability to prove the diagnosis by culture or staining of Koch's bacillus has not been held as disproof (Joll, 1952).

Although the literature would suggest that the disease is not too rare in Europe and America, no other case is recorded at St. Mary's Hospital, and only one other, by Keynes (1938), in the British literature, indicating the unlikelihood of the lesion being encountered frequently enough in clinical practice to be considered often in the differential diagnosis of thyroid swellings. Nevertheless, the recorded experience, together with our own experience of the lesion, suggests that even though an accurate pre-operative or even intra-operative diagnosis is not made, adequate treatment, as usually applied to solitary, benign thyroid swellings, is satisfactory.

SUMMARY

A case of isolated thyroid tuberculosis, presenting as and treated as a benign 'adenoma', but proving to be tuberculous, is recorded with comment on the unlikelihood of a pre-operative accurate diagnosis being made and the satisfactory management of the condition by standard measures.

Acknowledgements.—I am much indebted to Professor C. G. Rob for permission to treat this case and for his comments and help in its presentation. Also to Dr. Leslie Michaels for the pathological report; to Dr. Cardew of the St. Mary's Hospital Medical School Department of Photography for the photograph of the specimen; and to Mr. A. Beasley of the Department of Morbid Anatomy for the photomicrographs.

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PENETRATING WOUNDS OF THE SUPERIOR VENA CAVA

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PENETRATING wounds of the superior vena cava are rare.

Harris (1938) reported a case in which a stab wound half an inch long in the intrapericardial part of the superior vena cava caused death within a few minutes. The injured man had been able to make his way through a fence and walk thirty yards before dropping dead. Oram (1944) reported the case of a man who sustained a rupture across the intrapericardial part of the superior vena cava from injuries caused by falling off a pony. This man died within a few minutes.

Bigger and Wilkinson (1933) record a case of a wound of the superior vena cava which was sutured at operation: "This patient, admitted to hospital thirty minutes after he was stabbed in the right chest through the third costal cartilage, was found to have the syndrome of cardiac tamponade. An operation was performed and a wound one centimetre long, in the intrapericardial part of the superior vena cava, was sutured. Hæmorrhage was controlled while the incision in the vein wall was being sutured, by keeping the left index finger behind the vein."

In the case reported in this present paper there was a penetrating wound in the superior vena cava 1½ in. long. Not only did this injured man survive the two and a half hours before he was placed on an operating table, but he also made an uneventful recovery after the large slit into the superior vena cava had been closed by suture.

CASE REPORT

L. V. D. S., a male Sinhalese, aged 30, was admitted to the General Hospital, Colombo, on March 14, 1957, at 6.10 p.m. He had been sent from a place 9 miles away, where he had been stabbed in the right chest at 5 p.m. His pulse was thready and his extremities cold. He reached the emergency ward at 6.25 p.m. A dressing which had been placed over the wound was soaked with blood. The pulse was just perceptible at 140, and the blood-pressure was 60/50. The percussion note was dull over the right lower chest and the breath sounds were impaired. The patient was conscious, but in acute distress. A saline drip with noradrenaline was set up at once and blood taken for grouping and direct testing. The blood-pressure was maintained at 110 systolic by adjusting the rate of the intravenous drip.

The patient was placed on the operating table at 7.30 p.m., and a blood transfusion drip into another vein was now set up. After anæsthetizing the patient for a few minutes with nitrous oxide and oxygen (Dr. L. M. V. Attygalle) an endotracheal tube was passed, and the patient turned over on to his left side. The right fifth rib was resected and the right pleural cavity was opened through its bed. The pleural cavity was filled with massive blood-clots. The clots were evacuated and the upper lobe of the right lung was examined for a penetrating wound, but none was found. Blood was welling from the wall of the mediastinum above the root of the right lung, and when this area was exposed by wiping

away the blood and clots, there was vigorous bleeding from a wound 1½ in. long opening the superior vena cava along its long axis above the pericardium. The profuse bleeding at this stage called for immediate action. The expedient was adopted of grasping the two angles of the wound with the points of a pair of Spencer Wells artery forceps, and of apposing the edges of the wound in the vein by pulling up and elongating its edges by

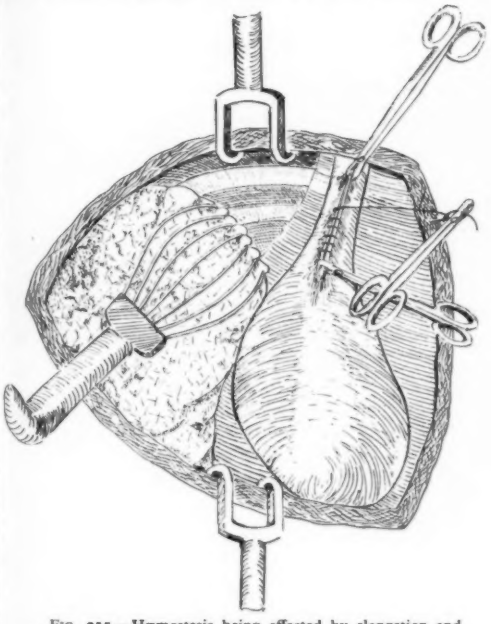

FIG. 215.—Hæmostasis being effected by elongation and elevation of the wound in the superior vena cava, while the wound is being closed by a continuous suture.

traction on the Spencer Wells artery forceps. This manœuvre proved completely successful in controlling the escape of blood from the vein. There was complete hæmostasis. The Spencer Wells artery forceps were maintained in position by the assistant, while the wound in the vein wall was closed by a continuous over and over suture of fine silk (*Fig.* 215). This suture arrested the bleeding. While the suture was being inserted, the stab wound in the chest wall was seen from within the pleural cavity. It was a vertical wound cutting right across the third costal cartilage about its middle. There was no bleeding from this wound.

A drainage tube had been inserted into the pleural cavity through a stab wound in one of the lower intercostal spaces, and this drainage tube was connected to an under-water seal. The opening made into the pleural cavity was closed. The muscles and skin overlying the chest at the original stab wound were also closed by suture. This stab wound was 1 in. long vertically disposed over the third right costal cartilage 1 in. from the border of the sternum. The scar of the wound is seen in *Fig.* 216.

One pint of blood was given to the patient at the operation and a further 1½ pints during the following night. The noradrenaline saline drip was continued till the next afternoon. The patient made an uneventful recovery from the operation, and was up and about in ten days. Subsequent inquiries established that the injured man had been stabbed with a dagger. The dimensions and the position of the entrance wound on the chest wall suggested that the dagger had been plunged into the right chest. The blade must have passed between the right lung and the mediastinum and the point of the blade must then have slit the superior vena cava down its long axis.

DISCUSSION

How did this man survive with a penetrating wound in his superior vena cava 1½ in. long which was not sutured till over 2½ hours after the injury?

FIG. 216.—Photograph of the patient three weeks later showing the scars of the stab wound and of the incision used for opening into the pleural cavity.

Although so much bleeding had occurred by this time that the patient was almost exsanguinated, there must have been some natural arrest of the violent bleeding that would occur from a wound of so large a vessel. The massive blood-clots overlying the slit in the wall of the vein had sufficed to stay the rush of blood, and the profuse bleeding which occurred when these clots were disturbed bears this out. The alarming hæmorrhage at this stage would have been fatal in a few minutes, had it not been controlled completely by the expedient of lifting up and elongating the wound in the vein wall by traction on its edges. The manœuvre was successful because of the low pressure in this vein. It was more practicable than grasping the wounded vessel with a clamp, and it secured complete hæmostasis while the wound in the vein wall was being closed by a continuous suture.

SUMMARY

A penetrating wound of the superior vena cava is reported. The injured man recovered after a surgical operation repairing the wound in the vein.

Acknowledgements.—I am indebted to Dr. Malinga Fernando, Research Assistant to the Professor of Surgery, whose prompt pre-operative management of this case contributed in large measure

to the success which was attained. He also collected the references to the injuries of the superior vena cava. The drawing (*Fig.* 215) was made by Mr. A. A. Mahawatte from sketches made by the writer soon after the operation.

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ISLET-CELL TUMOUR OF THE PANCREAS

REPORT OF A CASE IN A CHILD AGED 7 YEARS

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CONVULSIONS in children are so frequently due to fever or an intrinsic disorder of the central nervous system that there is a tendency to overlook other rarer causes. One of these is hypoglycæmia caused by an islet-cell tumour of the pancreas. We have been able to find only 7 reports of children under 10 years of age with this condition, and so wish to describe the case of a girl aged 7 years which presented some interesting features.

CASE REPORT

Carol M., aged 7 years 6 months, the tenth of eleven children, had been well until February, 1956. At this time she fell downstairs and was unconscious for a brief

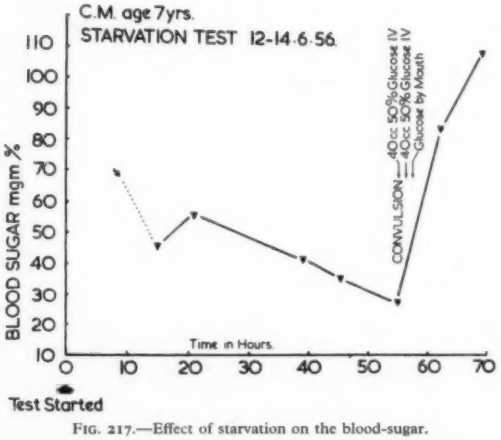

FIG. 217.—Effect of starvation on the blood-sugar.

period. Two months later she had a generalized convulsion lasting 5 minutes. She was admitted to Ruchill Hospital, where she was found to be drowsy, and appeared to have slight athetosis of the right arm. The knee and ankle tendon reflexes were absent. Apart from this, physical examination was negative. The urine contained acetone. A lumbar puncture was performed and the cerebrospinal fluid was found to contain 2 cells per c.mm., 15 mg. per cent of protein, and 21 mg. per cent of sugar. At this time no specific treatment was given, and 2 days later she appeared well, though there was a generalized muscular hypotonia. On the third day, however, she began to have numerous brief convulsions and her temperature, which had hitherto been normal, rose to 104° F. She required continuous anticonvulsant treatment and was semi-comatose for 3 days. During this time a further examination of the cerebrospinal fluid revealed a sugar content of 27 mg. per cent. A single blood-sugar estimation at the height of this episode was 146 mg. per cent. On the sixth day after admission her fever subsided and there was a gradual return to consciousness. Thereafter she had a slowly diminishing muscular weakness, and 23 days after admission she was discharged, apparently healthy. A lumbar puncture was performed just prior to discharge and revealed a sugar content in the cerebrospinal fluid of 57 mg. per cent, the highest found while she was in hospital on this occasion. These cerebrospinal fluid sugar levels presumably mimicked the blood-sugar levels, though the significance of this was not fully appreciated at the time.

During the next month she had two episodes of transient headache before breakfast, but there were no further symptoms until June, 1956. One morning, a few minutes after waking, and while still sitting in bed, she had a generalized convulsion lasting 3 minutes. On recovery she vomited and complained of frontal headache. She was re-admitted to Ruchill Hospital, where once again a full physical examination proved largely negative. A lumbar puncture revealed that the cerebrospinal fluid contained only 1 cell per c.mm., 50 mg. per cent protein, and 36 mg. per cent sugar. The blood-sugar 4 hours after admission was only 49 mg. per cent, despite the fact that she had been given glucose drinks, so a provisional diagnosis of hypoglycæmic convulsions was made.

She was transferred to Stobhill General Hospital under the care of Dr. I. D. Riley for further investigation. To establish that hypoglycæmia was, in fact, the cause of her convulsions, a starvation test was performed (*Fig.* 217). She was given nothing but water, and after 55 hours had a brief generalized convulsion. Her blood-sugar at this time had fallen to 28 mg. per cent. She was immediately given 40 ml. of 50 per cent glucose solution intravenously, and received another 40 ml. over the next hour; 1½ hours later she had fully recovered. A blood eosinophil count a few hours after her convulsion was 67 per c.mm.

Other investigations were as follows: Serum bilirubin, 0·6 mg. per cent; alkaline phosphatase, 14·0 units; proteins, 6·3 g. per cent; thymol turbidity, negative; chlorides, 109 mEq./l.; potassium, 4·28 mEq.; sodium,

139 mEq.; calcium, 11·9 mg. per cent. A blood-sugar curve was normal. An electro-encephalogram showed episodes of slow activity from the left side.

On these findings a diagnosis of islet-cell tumour of the pancreas was made.

A few weeks after admission and shortly before a proposed exploratory operation, the patient had another generalized convulsion. Rather surprisingly the blood-sugar at this time was 114 mg. per cent and there was little response to intravenous glucose solution. Despite this, it was felt that a laparotomy was justified.

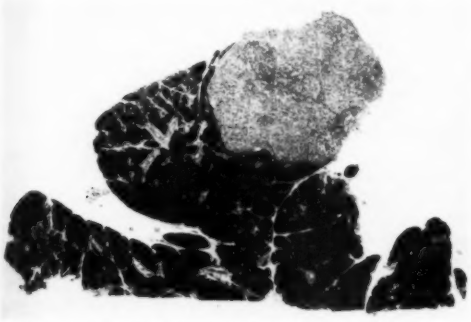

FIG. 218.—Section of pancreas showing the islet-cell tumour. (× 2·5.)

AT OPERATION (J. P. G., July 12, 1956).—The abdomen was opened through a transverse incision about 1½ in. above the umbilicus. Both rectus muscles were cut across and the wound extended into the flanks by section of the muscles in the line of the incision. The pancreas was exposed through the gastrocolic omentum, and there a tumour mass was found about 1 in. from the tail, about 1½ cm. × 1 cm., lying superficially, and resembling in colour and consistency an enlarged lymph-node. This small mass which was arising from the pancreas was presumed to be an islet-cell tumour and to be causing the symptoms. The dissection was begun from the tail of the pancreas and continued without any difficulty or undue hæmorrhage towards the neck. The body and tail of the pancreas having been freed, the organ was sectioned just distal to the superior mesenteric artery and the freed portion of pancreas removed. The stump was closed in the first place by continuous fine catgut suture of sewing-machine type and the capsule sutured by fine interrupted silk stitches. Although the section of the pancreas had been made in the form of a wedge, a very accurate closure was not found to be possible, but on completion of the suture layers hæmostasis was found to be perfect. A small cigarette type of drain was inserted to the bed of the pancreas, the gastrocolic omentum was closed, and the abdominal incision sutured by fine interrupted silk to all layers, except skin, which was closed by interrupted nylon stitches. The drain was brought out through the centre of the wound.

In the period of starvation prior to the operation, the blood-sugar was estimated hourly, and following operation these observations were continued rather less frequently. At no time did the blood-sugar fall below 110 mg. per cent.

HISTOLOGICAL EXAMINATION (Dr. H. MacDonald Cameron).—The specimen was typical of a benign islet-cell tumour (*Figs.* 218, 219). The cells were uniform and showed no pleomorphism or excessive mitotic activity, and there was a well-formed capsule. Throughout the growth there was an unusual degree of hyalinization between the strands of cells. In the adjoining pancreas there was a very large amount of islet tissue, but this appeared normal morphologically.

The child's convalescence was completely uninterrupted. The drain was removed after 48 hours and the wound healed by first intention. It was, in fact, noticeable how little discomfort the child appeared to have from the very large transverse incision. She was very active in her bed on the day following operation and was discharged from the Surgical Unit on the fourteenth day.

Three weeks after her operation the child was subjected to a further starvation test, lasting 48 hours.

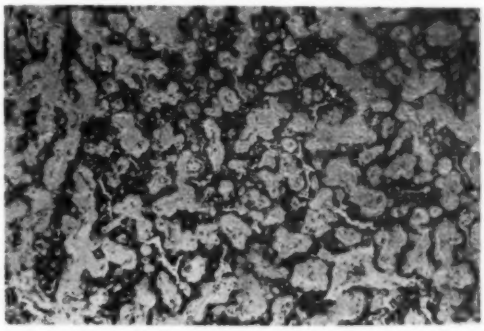

FIG. 219.—Higher-power view of the tumour seen in *Fig.* 218.

During this time she had no symptoms. At the end of the test the blood-sugar had fallen to 49 mg. per cent.

She was discharged early in August, 1956, but a few weeks later was admitted to another hospital, having had a further generalized convulsion. No evidence of hypoglycæmia was found, and a further electro-encephalogram still only showed some left-sided changes of doubtful significance. Treatment was started with primidone 0·25 g. thrice daily, and since then she has had no further convulsions.

DISCUSSION

An islet-cell tumour of the pancreas in a child presents special problems, some of which were encountered in our case.

The diagnosis will usually be made in two stages. First, the recognition of hypoglycæmia, and next the elimination of other causes of this metabolic disturbance. Achievement of the first stage may be the more difficult. In adults Skillern and Rynearson (1953) have shown that hypoglycæmia may cause a great diversity of symptoms, such as varying degrees of loss of consciousness, convulsions, sweating, transient neurological disturbances, hunger, and headache. As children readily become hypoglycæmic, they may be expected to present the more dramatic features, and so this first stage will most often be reached if the blood-sugar is estimated in all cases of recurrent convulsions. Since the body's mechanisms for preventing hypoglycæmia, and thus protecting the brain, are powerful, the period of hypoglycæmia may be short.

Having once established that hypoglycæmia exists, there are, theoretically, many possible causes. Conn (1947) has divided these into: (1) Organic, in which he includes islet-cell tumours, liver disease, pituitary and adrenal dysfunction, and lesions of the central nervous system; (2) Functional, the commonest type in adults; and (3) Miscellaneous, including causes as yet unexplained by present methods of investigation. Though this presents a formidable

list, in children it should be possible to exclude many on the history and clinical examination. For instance, disease of the liver, adrenals, or pituitary will affect growth or have other obvious clinical signs, and functional hypoglycæmia usually occurs after, rather than before, meals. In cases of doubt, liver function tests and an adrenaline–blood–glucose test will exclude liver disease, and an adrenaline–blood–eosiniphil test adrenal or pituitary disease. A glucose tolerance curve will show an abnormal fall between the second and fourth hour in functional hypoglycæmia (Conn, 1947). Some of these tests were performed in our case, but not the adrenaline–blood-sugar and eosiniphil curves, since we felt that adrenal and pituitary disease could be excluded on clinical grounds.

If an islet-cell tumour is still suspected the response to starvation will help to establish the diagnosis. Hitherto it has been customary to starve the patient, but not to withhold fluids, for only 24 hours. More recently periods of up to 72 hours have been recommended (Breidahl, Priestley, and Rynearson, 1956) since symptoms have not appeared within 24 hours in cases later found to have a tumour. This was true in our case since no symptoms appeared for 55 hours and at 21 hours the blood-sugar had only fallen to 56 mg. per cent. It is difficult to explain why a relatively short overnight fast produces symptoms in some circumstances, while in others a lengthy fast of 48 hours or more is required, and we can only assume that this condition is phasic, like many others. The lowest blood-sugar found during this test has varied in established cases, but most authors are agreed that only figures below 50 mg. per cent are significant and that symptoms are not usually encountered above 40 mg. per cent.

In children, the presence of an islet-cell tumour cannot always be presumed when convulsions are found in association with hypoglycæmia. Darrow (1936) has reported finding intermittent hypoglycæmia in two mentally retarded children who were having convulsions. He did not consider that the mental state was the result of the hypoglycæmia, but rather that there was a general disturbance of the brain, of which hypoglycæmia and mental defect were the main features. Furthermore, McQuarrie (1954) has described some very young children who suffered idiopathic spontaneous hypoglycæmia, possibly due to a disturbance of the alpha-cells of the pancreas, and who responded well to corticotrophin.

The decision to operate may be difficult because of these uncertainties. In adults, Whipple (1944) has suggested that three criteria should be fulfilled: (1) The attacks should occur while fasting; (2) During an attack, or after fasting, the blood-sugar should be under 50 mg. per cent; (3) The attack should respond readily to glucose. In children the hazards of continuing attacks of hypoglycæmia are possibly greater than in adults. Hubble (1957) has pointed out that such episodes are more difficult to manage at this age because of the ascendancy of the anabolic hormones, and numerous authors have shown that serious brain damage may occur (Talbot, Sobel, McArthur, and Crawford, 1952; Hoff, Grenell, and Fulton, 1945; McQuarrie, 1954). Our case appears to have sustained brain damage, despite early removal of the tumour. Two of the fits, one before and one after operation, occurred without hypoglycæmia, and we have presumed that these were due to such damage, since similar symptoms are known to occur in diabetic children who have insulin reactions (Talbot and others, 1952).

If at operation no tumour mass is obvious, despite a thorough search of the whole of the pancreas, it appears reasonable to resect the pancreas to about the level of the superior mesenteric vessels, since these tumours may be so small that they are only revealed in serial sections, and, in the case of the child at least, the lesion is most likely to be situated in the tail. The dissection of the pancreas in our case presented no difficulty, and indeed, a simple enucleation of the tumour might have been sufficient.

SUMMARY

A case of islet-cell tumour of the pancreas in a girl of 7 years is described.

She suffered recurrent hypoglycæmic convulsions, and brain damage probably occurred despite early removal of the tumour.

The difficulties of diagnosis and the special dangers of hypoglycæmic attacks in children are discussed.

We should like to thank Dr. H. MacDonald Cameron for examining the tumour histologically, Drs. I. D. Riley and J. H. Lawson for their assistance in preparing the paper, and Mr. P. S. Waldie for the photomicrographs.

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INTESTINAL OBSTRUCTION IN PREGNANCY DUE TO VOLVULUS OF THE CÆCUM AND ASCENDING COLLON

By D. E. STURDY and T. McG. McNIE
R.A.F. HOSPITAL, RINTELN, GERMANY

The earliest recorded case of intestinal obstruction in pregnancy was by Houston in 1830. Pregnancy ileus, as a cause of intestinal obstruction, has been adequately described in world literature, and Slemon and Williams (1938) published over 1000 references. Hansen (1941) collected 84 cases of intestinal obstruction in pregnancy in the English literature and added a case of his own. Since that time other cases have been recorded by Andreasen (1941), Barone, Power, and Kuhn (1941), Hipsley (1942), James (1946, 1950), Siegel and Pleshette (1948), Matthews and Mitchell (1948), and Baker and Lister (1953). The comparative rarity of this condition has stimulated the authors to describe a further case in which the precise nature of the malrotation causing volvulus was ascertained at operation.

CASE REPORT

Mrs. J. C., aged 21, a primigravida 32 weeks pregnant, was admitted to hospital on Aug. 30, 1953. The pregnancy had been uneventful until 7 days before admission, when she began vomiting, which became profuse and which was accompanied 3 days later by severe colicky upper abdominal pains, not uterine in origin. She had not had a bowel action for 5 days. She had been under observation at the R.A.F. Hospital, Rostrup, for 2 days and had been given sedatives, and 3 pints of glucose saline to combat dehydration.

On examination she looked ill, was vomiting, and complained of pain; her tongue was moist but furred. The temperature was 99° F. and pulse-rate 94/min.; blood-pressure was 140/80. There was no visible peristalsis, but the upper abdomen was distended and hyperresonant. The fundus of the uterus was 2 in. above the umbilicus. The right hypochondrium was tender, and faint bowel-sounds were heard, which were not obstructive in character. The uterus was contracting feebly, but the contractions were not related to the attacks of abdominal pain. The rectum was empty and ballooned, and there was tenderness on pressure over the cervix.

After 4 hours' observation, as her condition was not improving, a laparotomy was advised. The pre-operative diagnosis had not been established, but the differential diagnosis rested between intestinal obstruction, acute appendicitis, salpingitis, torsion of an ovarian cyst, and pregnancy ileus.

At Operation (D. E. S. and T. McG. McN.).—Under general anæsthesia the abdomen was explored through a long right paramedian incision. The cæcum, ascending colon, and one-third of the transverse colon were enormously distended, bloodless, and a volvulus had occurred round the pedicle of the ileocolic and right colic arteries. A derangement of intestinal rotation was recognized, the transverse colon passing through a gap behind the superior mesenteric artery and root of the mesentery (*Fig.* 220). The pedicle composed of the ileocolic and right colic arteries was ligated and the nonviable portion of the large gut, together with the terminal 10 in. of the ileum, was resected. The proximal end of the transverse colon was released from the gap in the root of the mesentery and invaginated. The patient's poor condition precluded an immediate ileotransverse anastomosis, so a terminal ileostomy was fashioned round a Paul's tube. The paramedian incision was closed in layers with catgut, and thread sutures were used for the skin. Two pints of blood were given during the operation and intravenous therapy and gastric suction continued for 5 days afterwards. On the seventh day the ileostomy was working well and the patient's general condition was very satisfactory. On the fourteenth post-operative day she went into labour. There was delay in the second stage due to a mid-cavity transverse arrest of the fœtal head. Episiotomy was performed, the head manually

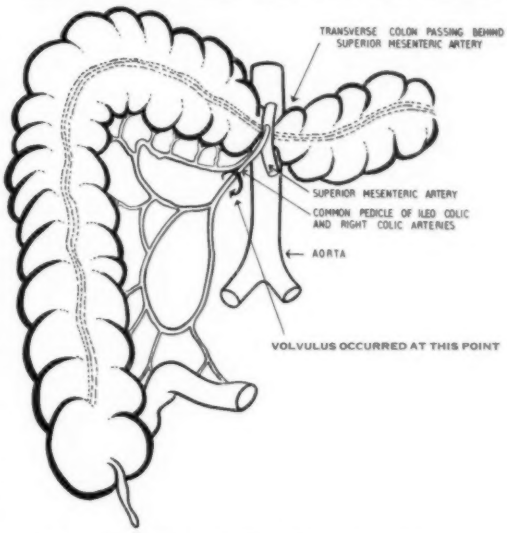
TRANSVERSE COLON PASSING BEHIND SUPERIOR MESENTERIC ARTERY
SUPERIOR MESENTERIC ARTERY
COMMON PEDICLE OF ILEO COLIC AND RIGHT COLIC ARTERIES
AORTA
VOLVULUS OCCURRED AT THIS POINT

Fig. 220.—Diagram to illustrate the vascular arrangements and anomaly of intestinal rotation found at operation.

rotated, and forceps delivery of a healthy living male infant, weighing 3 lb. 13 oz., was effected (P. M. Healey). After labour, which had lasted 36 hours, the patient was severely dehydrated, so an intravenous dextrose saline infusion was given and continued until her death 3 days later. The day after delivery she became very lethargic, and her general condition deteriorated, and she died on Sept. 16, 1953. Post-mortem examination was refused by the husband.

EMBRYOLOGY

Dott (1923) gave a masterly description of the anomalies of intestinal rotation. During reduction of the physiological hernia at the tenth week, rotation of the gut occurs around the axis of the superior mesenteric artery. Derangements of reduction in this second stage lead to:—

1. Non-rotation of the midgut loop, where the cæcum and colon are on the left side of the abdomen.

2. Reversed rotation of the midgut loop, where the transverse colon passes behind the superior mesenteric artery.

3. Malrotation of the midgut loop, i.e., irregular defects in rotation.

The type of rotation found at operation in our case belonged to Group 2 of Dotts's classification. The lack of fixation of the cæcum and ascending colon to the posterior abdominal wall, together with displacement of the gut by the enlarging uterus, predisposed to volvulus formation.

DIAGNOSIS

Smith and Bartlett (1940) reported one case of intestinal obstruction in 66,431 deliveries at the Boston Lying-in Hospital, and Weintraube and Jaffe (1940) mentioned 3 antepartum cases in 32,000 deliveries. Obstruction is commonest in the 4th, 5th, 8th, and 9th months, and adhesions and bands accounted for 44 per cent of Hansen's (1941) collected series. Seventeen per cent of the obstructions in this series was due to volvulus. There is no relationship between the patient's age or fecundity with the incidence of obstruction (Matthews and Mitchell, 1948). Twenty-five per cent of patients give a history of a previous abdominal operation (Hansen, 1941). Diagnosis is notoriously difficult and abdominal pain, vomiting, distension, and constipation are found in varying degree in different patients. In our case vomiting was the first symptom to be followed in 3 days by colicky abdominal pain and distension, and the patient had been constipated for 5 days. On these symptoms alone intestinal obstruction should be strongly suspected. On examination, a distended tympanitic upper abdomen, with obstructive bowel-sounds and with a normal or slightly raised pulse-rate, and a normal temperature should confirm the diagnosis. The differential diagnosis includes ileus of pregnancy, acute appendicitis or salpingitis, torsion of an ovarian cyst, strangulated external or internal hernia, and peritonitis from any cause. A straight radiograph of the abdomen may be useful in demonstrating gaseous distension of the affected intestine. If there is any doubt, laparotomy should be advised, as the maternal mortality for neglected cases is in the region of 31 per cent and the fœtal mortality 57 per cent (Hansen, 1941). Prompt surgical intervention offers the best hope of reducing the fœtal and maternal mortality rate of this rare but serious complication of pregnancy.

SUMMARY

1. The literature on intestinal obstruction in pregnancy is briefly reviewed and a further case is recorded.

2. The embryological basis for derangements of intestinal rotation is described.

3. The diagnosis of this serious complication of pregnancy is discussed.

We are indebted to Flying Officer P. M. Healey and the Nursing Sisters of the R.A.F. Hospital, Rinteln, for their hard work and co-operation with the treatment of this case. We would also like to thank Dr. J. O. Earle, of the Royal Masonic Hospital, for the illustration, and the Director General of the R.A.F. Medical Services for his kind permission to publish this case.

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REVIEWS AND NOTICES OF BOOKS

Sir Charles Bell: His Life and Times. By Sir GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S., Honorary Consultant Surgeon to the Middlesex Hospital; and E. W. WALLS, M.D., Ch.B., B.Sc., F.R.S.(Ed.), S. A. Courtauld Professor of Anatomy in the University of London at the Middlesex Hospital Medical School. 8¾ × 6 in. Pp. 288 + xii, with 49 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 42s.

IN the preface the authors justify this book by saying that although the name of Sir Charles Bell is familiar to all who follow the profession of medicine owing to its being coupled eponymously with anatomical structures and clinical states, yet "there must be many other than those privileged to work in the Hospital which Bell served for more than twenty years, or in the Medical School which he above all others called into being, who would wish to know what manner of man he was and the measure of his achievement. To provide an answer is the main purpose of this book."

The Hospital is the Middlesex Hospital, founded in 1745 as the Middlesex Infirmary "for the sick and lame of Soho", in Windmill Street, off Tottenham Court Road, in two small houses with accommodation for fifteen patients and three beds for accident cases.

Charles Bell, born in 1774, was the youngest of four boys. His mother must have been an extraordinary woman, for although left a widow with slender means in 1779, all four sons became well known not only in Edinburgh, their native city, but very widely elsewhere. The eldest son, Robert, became Professor of Conveyancing to the Society of Writers to the Signet. The second, John, "who trained Charles in anatomy and surgery, was the most outstanding surgeon in Edinburgh at the close of the eighteenth century". The third son, George, became the "Professor of Scots Law in Edinburgh and acknowledged one of the greatest masters of commercial jurisprudence of his time". Charles, the subject of this book, who was "destined to make the name of Bell known throughout the world", in 1828 was appointed the first Professor of Surgery in the newly founded University of London, and in 1836 accepted the invitation to occupy the Chair of Surgery in the University of Edinburgh. He died at Worcester in 1842.

The family must have been very united, judging by the surviving records, but it was the mother's influence in the education, training, and outlook of her boys which resulted in their subsequent eminence. Charles owed much in later life to the foresight of his mother, who, while he was a boy, had his natural artistic talents and aptitude trained and developed by David Allan, the painter. Charles, after leaving the High School of Edinburgh at the age of 18, was apprenticed for five years to his brother John, a Surgeon Apothecary in Edinburgh, and attended the lectures of Alexander Monro (*secundus*) in the University. John, in addition to his practice, had a private anatomy school in Edinburgh and taught Charles both anatomy and surgery and he, for his part, was able to assist John in writing a book on *The Anatomy of the Human Body* (1797–1804), the second volume of which had illustrations of the arteries drawn by him. He had also contributed the description of the nervous system. The Monros, both *primus* and *secundus*, were not operating surgeons, so John Bell's contribution to anatomical studies, assisted by Charles, was such that "the subject of surgical anatomy seems to have been given its birth by him".

The anatomical and surgical teaching of John Bell was so popular in Edinburgh that it aroused the jealousy of a university clique led by James Gregory, the University Professor of the Practice of Medicine. The result was that in 1799 John gave up teaching and thenceforth confined his work to the practice of surgery, though neither John nor Charles, who had taken over the school and been admitted a member of the College of Surgeons on Aug. 1, 1799, was allowed to operate in, or attend the autopsies at the infirmary. Charles, realizing that he had little hope of success in Edinburgh, on the advice of his brothers decided to go to London, which he did on Nov. 23, 1804. He had already published books on anatomy while still a student, he had considerable skill in drawing and modelling anatomical and clinical specimens, and although his financial resources were meagre, his knowledge of anatomy and surgery, together with his artistic talent and ability, should have had a real value in London. He was received amicably by such surgeons of repute as John Abernethy and Astley Cooper, but no appointment was offered him. He applied unsuccessfully to James Wilson, the successor to the Hunters, and Matthew Baillie, at the Great Windmill Street School of Anatomy. During his first year in London he completed the plates for the illustrations of his book *Essays on the Anatomy of Expression in Painting* which was published in 1806. "Although written primarily for painters on the theme 'Expression is to passion what language is to thought', the book is a notable contribution to medical literature from the point of view of both human and comparative anatomy."

In 1805 Bell decided to open a private school of anatomy and secured old but commodious premises at Nos. 10 and 11 Leicester Street. In October he advertised the syllabus of the classes, as had James Douglas (1707), William Cheselden (1713), and William Hunter (1746). The classes in anatomy, both theoretical and practical, were for artists and medical students; for the latter there was a course of demonstrations in operative surgery on the cadaver.

In addition to teaching he was busy writing a two-volume *System of Operative Surgery*, the first being published in 1807. His activities in London were interrupted in 1809 when the wounded from Corunna were brought to Portsmouth. He immediately volunteered his services which were accepted by the Medical Board and he worked in the hospital at Haslar. In 1811 Bell married Miss Marion Shaw, the sister of his brother George's wife, and of John Shaw, one of his house pupils who later became his assistant. He had moved from Leicester Street into Soho Square just before his marriage, probably to be in the vicinity of other private anatomy schools and a district popular with artists.

In 1765 William Hunter, having unsuccessfully petitioned the Government to provide a site for him on which he, at his own expense, could erect a national theatre of anatomy, built one in Great Windmill Street. This became the best known and most successful school in London and was occupied by William Hunter until his death in 1783. He left it to his assistants, Matthew Baillie and William Cruikshank; the former sold his share to James Wilson in 1799; after Cruikshank died in 1800, James Wilson carried on the school, with the assistance of Benjamin Brodie. This was the position when Charles Bell came to London. In 1812 James Wilson offered to transfer the school to Bell; when satisfactory terms had been arranged the latter found himself the proprietor. The school became a great success; he was encouraged in his work by many who were, or in the future would become, well-known surgeons. He was admitted a Member of the Royal College of Surgeons of London in 1813. In March, 1814, Charles Bell was elected by the

Board of Governors to fill a vacancy on the surgical staff of the Middlesex Hospital. Now that he was a recognized surgeon, his School of Anatomy and the hospital both benefited by attracting the same students, and the association became even closer when John Shaw, his assistant in the school, was also appointed to the staff of the hospital. Bell was now fully engaged in hospital work, preparing lectures, dissections, and models. His book on operative surgery attracted the military surgeons to attend the surgical practice in the hospital, which was also visited by surgeons from all parts of Europe and overseas. The type of surgery in vogue in London at this time was given in detail by the late Sir John Thompson Walker in his Presidential Address to the Medical Society of London on Oct. 9, 1933, with the title "Surgery in the Early Nineteenth Century". This was based on the diary of John G. Crosse, a house pupil of Bell's, who attended St. George's Hospital for his surgical instruction (1811–13). The address is published in the *Transactions* of the Society.

Immediately after the Battle of Waterloo (June 18, 1815) Bell and his brother-in-law John Shaw went to Brussels and did much valuable surgical work for the wounded. Bell's records, with accompanying illustrations, are in the possession of the Royal College of Surgeons of Edinburgh.

The knowledge of the nervous system has to a large extent developed independently of other branches of physiology. Reference to the bibliography of Charles Bell, given by the authors at the end of this book, shows that, even when a student and assistant to his brother John, he was always interested in this subject. He had contributed an article on it in his brother's *Anatomy of the Human Body* (1797–1804); it was also the underlying medical interest in his own essays on the *Anatomy of Expression in Painting* (1806). His claim to priority in the functions of the anterior and posterior roots of the spinal cord has been the subject of prolonged controversy. He formulated his ideas in 1811 in a privately printed pamphlet entitled *A New Idea of the Anatomy of the Brain submitted for the Observation of his Friends*. Only two copies of this pamphlet are known to exist, but it can be read in *Selected Readings in the History of Physiology* (edited by John F. Fulton, published by Baillière, Tindall & Cox, 1930). In this tract Bell demonstrated the motor functions of the anterior roots but did not prove the sensory functions of the posterior. François Magendie (1783–1855), the pioneer experimental physiologist of France, began in 1821 to publish the first French journal devoted to physiology. In the second volume he published two papers on the functions of the roots of the spinal nerves in which he claimed his discovery of the sensory functions of the posterior roots. Bell responded immediately by claiming in an article in the *Transactions* of the Royal Society that he had discovered the functions of the spinal roots in 1811. These articles led to what the late Professor J. M. D. Olmsted, the biographer of Magendie, called "The Bell–Magendie Controversy". The battle was taken up by John Shaw and Herbert Mayo (1796–1852), both of whom had been Bell's assistants.

The authors of the book under review give the full details of this controversy and in the preface acknowledge the help they have received from the widow of Professor Olmsted. Their conclusion is that "the right of discovery of the distinct functions of the nerve roots may surely be given in some measure at least to Bell and his assistants".

The success of the Great Windmill School under the direction of Bell was such that it assumed the position of the Medical School for the Middlesex Hospital. In 1824 Bell was appointed Professor of Anatomy and Surgery at the Royal College of Surgeons. This was a further inducement for students to enter the Windmill Street School for anatomy and the Middlesex Hospital for clinical work. Bell was given the Order of Knighthood of the House of Guelph (Knight of Hanover), and his reputation was such that when the University of London was founded (1828) Lord Brougham, one of his early Edinburgh friends, persuaded the University to appoint him Professor of Surgery, with the Senior Physician at the Middlesex, Dr. Thomas Watson, as Professor of Medicine; Bell then resigned from the Windmill Street School. The Council of the University of London in 1828 put an advertisement in *The Times* informing medical students of the University that they were at liberty to attend the Middlesex Hospital for their clinical instruction. The Board of the Hospital had not been informed about this advertisement and, the University being non-sectarian, they feared that, unless it was denied by them, many of the six hundred governors would cancel their subscriptions. The result was that Bell resigned the professorship, so the University built its own hospital. The staff of the Middlesex, fearing that this step by the University might affect the status of the Hospital as a medical school, petitioned the Board, which agreed to establish their own complete medical school. The introductory address given by Sir Charles Bell in October, 1828, at the opening of the University of London, and that on Oct. 1, 1835, at the opening of the Middlesex Hospital Medical School, are both given in the appendices of this book. Before the end of 1835 he had accepted the invitation to occupy the Chair of Surgery in the University of Edinburgh. In 1833 Sir Charles Bell, together with Sir Astley Cooper, was awarded the M.D. (*honoris causa*) of the venerable Georg August University of Göttingen, with the Faculty of Medicine of which University will always be associated the name of Albrecht von Haller (1708–77). Recently, the Faculty of Pure Science of this University has played a predominant part in the development of nuclear physics and aerodynamics.

In 1842 Bell died a poor man and the Prime Minister, Sir Robert Peel, had to grant his widow a pension of £100 per annum, which was considered not only meagre but mean, considering what her husband had done for the science of medicine and surgery. The views of the *London Medical Gazette* are given in the appendix to the present biography.

This fascinating book is not only a record of medical education, practice, and research in the first half of the nineteenth century, but it is also a social history of the professional classes at that time. The reason given by the authors in the preface for the conception of the book is fully justified by its exposition. There is only one slip to be detected, namely, when the two Scottish authors, quite rightly, drawing attention to the debt of anatomy to their native land, give Ayrshire instead of Lanarkshire the credit for the production of William and John Hunter. The illustrations and format of the book are of the high standard expected from the publishers.

The Year Book of Neurology, Psychiatry, and Neurosurgery (1957–8 Series). Neurology edited by ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois; Psychiatry edited by S. BERNARD WORTIS, M.D., Professor of Neurology and Director of Psychiatric and Neurologic Services, University Hospital, New York; Neurosurgery edited by OSCAR SUGAR, M.D., Associate Professor of Neurological Surgery, University of Illinois. $7\frac{3}{4} \times 5$ in. Pp. 624, with 104 illustrations. 1958. Chicago: The Year Book Publishers Inc. $8.00.

LIKE our *Medical Annual*, the year-books from America are of great value to busy practitioners not only because of their collected abstracts but also by reason of the well-edited comments on recent developments. There are three editors of the three sections, neurology, psychiatry, and neurosurgery, which comprise this book, Roland P. Mackay, G. Bernard Wortis, and Oscar Sugar,

respectively. A wide field is covered by chapters on such diverse subjects as convulsive disorders, military neuropsychiatry, and surgery for involuntary movements. It is interesting to note that for the first time since the war the number of the mental hospital population in the United States has declined. That glia is an active agent in neural function rather than a mere supporting structure may surprise some readers. The reported successes in chemopallidectomy for Parkinsonism are heartening, but require confirmation. A. B. Savin, of the University of Cincinnati, shows that the claims for the Russian multiple sclerosis virus are false and that their virus is in reality that of rabies with no relationship to multiple sclerosis.

Although surveys of literature are wide, the editor of the section on neurosurgery tells us that there are no articles from the U.S.S.R.; none has been made available although the editors of the *Journal of Neurosurgery* have left an open door for them.

We were a little disappointed to find no references to cervical spondylosis or to the carpal tunnel syndrome, but there must obviously be a limit to any field reviewed and there is a very great deal of condensed and highly interesting material in this volume which should appeal to medical readers generally, whether or not they are practitioners of the particular specialties reviewed.

Extracorporeal Circulation. Compiled and edited by J. GARROTT ALLEN, assisted by FRANCIS D. MOORE, ANDREW G. MORROW, and HENRY SWAN. 9 × 6 in. Pp. 518 + xxii, with 190 illustrations. 1958. Springfield, Illinois: Charles C. Thomas (Oxford: Blackwell Scientific Publications). 57s. 6d.

THIS volume consists of a large series of articles by contributors from many of the surgical clinics in America, Sweden, Canada, and London.

The various pumps and oxygenators in use on both sides of the Atlantic are well described and illustrated.

The physiology of perfusion is discussed in detail and the problem of flow meters and their various types is explained in full. The effect of perfusion on various organs of the body is explained in minute detail and the investigation into the problems of coagulation is very thorough. A large part of this book, as one would expect, is devoted to the heart and its various congenital defects and how these can be treated with surgery while the patient's circulation is extracorporeal.

The different chapters are well illustrated by some one hundred and ninety drawings, photographs, and graphs.

With the rapid increase in the number of heart operations which are being performed to-day with extracorporeal circulation, this book will be found most valuable, for it contains a complete and up-to-date account of the many ways of dealing with every aspect of this interesting form of circulation.

Physiologists as well as anæsthetists and surgeons will find this book most valuable.

The Excitable Cortex in Conscious Man. By WILDER PENFIELD, O.M., C.M.G., Litt.B., M.D., D.Sc., F.R.C.S., Hon. F.R.C.P., F.R.S., Director of the Montreal Neurological Institute, McGill University, Montreal, Canada. The Sherrington Lectures, No. 5. 8½ × 5½ in. Pp. 42 + x, with 15 illustrations. 1958. Liverpool: Liverpool University Press. 10s. 6d.

THIS is the fifth Sherrington Memorial Lecture delivered by Professor Wilder Penfield at the University of Liverpool, the Council of which have established a biennial lectureship in recognition of the fact that Sherrington was Holt Professor of Physiology in the University from 1895 to 1913. An introductory tribute to Sherrington is followed by the presentation of the distinguished lecturer's views on the "centrencephalic system" and an account of some of his findings on cortical stimulation of conscious individuals. Currents of threshold strength apparently both inhibit and activate, interfering with the ability to make normal functional employment of the local area of cortex stimulated and at the same time activating some distant related ganglionic mechanism. The motor convolution which in 1870 Fritsch and Hitzig first stimulated electrically and mapped out is not the only cortical area with motor function and movements may be elicited from supplementary areas in temporal and parietal lobes, but there is an instability of response to stimulation. Penfield's experiments lead him to suspect that the ganglionic patterns of experience may lie in the hippocampus. As a further contribution to the how and why of action and recollection this makes interesting reading.

Surgery of the Chest. By JULIAN JOHNSON, M.D., D.Sc.(Med.), Professor of Surgery, School of Medicine and Graduate School of Medicine, University of Pennsylvania; and CHARLES K. KIRBY, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania. Second edition. 8¼ × 5½ in. Pp. 398, with 86 illustrations. 1958. Chicago: The Year Book Publishers Inc. 73s.

THE second edition of this handbook of operative surgery has been brought up to date, for much has happened in the surgery of the chest in the last four years.

The eighty-six plates which illustrate this volume are very informative and well drawn; only essential details of the operative technique are included.

All the operations of established value are portrayed and the text is written in a direct and lucid style.

For the young surgeon who wants safe information regarding operative technique inside the chest, this book could not be bettered.

Lumbar Disk Lesions. Pathogenesis and Treatment of Low Back Pain and Sciatica. By J. R. ARMSTRONG, M.D., M.Ch., F.R.C.S., Orthopædic Surgeon to the Metropolitan Hospital and Lambeth Hospital. With a Foreword by H. OSMOND-CLARKE, C.B.E., F.R.C.S., Orthopædic Surgeon, London Hospital. Second edition. 9¼ × 6¼ in. Pp. 244 + xii, with 60 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 45s.

THE second edition of this monograph, appearing as it does some six years after the first, contains a more conservative and confident approach to the treatment of low back pain and sciatica. The author's sane approach to the important problem of lumbar disk lesions is stimulating and reassuring. The numerous illustrations have been well chosen and do enhance the text.

Throughout the pages of this book the emphasis is on treatment, and this is what the practitioner wants to know.

There can be little doubt that this sound monograph will continue to take its place as the best that has so far been published on this important, and all too common condition.

Operative Surgery. Edited by CHARLES ROB, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London; and RODNEY SMITH, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Vol. VII. 10$\frac{9}{16}$ × 8¾ in. Part XIV, Breast, Pp. 5–42; Part XV, Genito-urinary System, Pp. 5–273. The volume is fully illustrated and indexed. 1958. London: Butterworth & Co. (Publishers) Ltd. 110s.

THE seventh volume of this comprehensive work deals with the surgical diseases of the breast and the genito-urinary system.

Victor Riddell, who writes on radical mastectomy, has many original and superb illustrations; it is quite refreshing and stimulating to read this section. The technique of mammaplasty is well described by Elliott Blake.

The operative surgery of the whole of the genito-urinary system is covered and illustrated in an excellent fashion. Each section is complete in itself and many of the illustrations are original.

The seventh volume of this surgical work is on the same pre-eminent level as the other volumes and is a real credit to British surgery.

The Early Diagnosis of the Acute Abdomen. By Sir ZACHARY COPE, B.A., M.D., M.S. (Lond.), F.R.C.S. (Eng.), Consulting Surgeon, St. Mary's Hospital, Paddington. Eleventh edition. $8\frac{3}{4} \times 5\frac{1}{2}$ in. Pp. 188 + xiv, with 36 illustrations. 1957. London: Oxford University Press. 18s.

SINCE its first publication in 1921 this book has become a classic, and it has not lost that status, as so often happens, by the appearance of many new editions. The essential principles of diagnosis are as clearly stated as before; the addition of new matter has only served to keep it up to date with recent discoveries, and although the text has increased, the number of pages is lessened by judicious resetting. New chapters have been added on the grouping of symptoms and on symptoms due to vascular lesions; neonatal intestinal obstruction receives greater mention and the general revision has been thorough. The diagrams remain clear and simple and the new radiographs are all to the point.

Any criticism can only be so small as to emphasize the general excellence of the book. We wonder if a wax-tipped bougie is ever used now to diagnose a stone in the ureter; the possible rise in blood-pressure as well as in blood-urea when a dissecting aneurysm involves the renal arteries might have been stressed. Some repetition is inevitable in such a work, but it serves to impress the fundamental points and to make each chapter complete in itself. Whether he writes in prose or in verse, Sir Zachary's style is always both elegant and readable and is maintained in this eleventh edition. The modest price of the book keeps it within the range of students as well as practitioners, and it should be read by all of them.

Lithiase de la Voie Biliaire Principale. By PABLO-L. MIRRIZI, Professor at the University of Cordoba (Argentina). $10 \times 6\frac{1}{2}$ in. Pp. 162, with 79 illustrations. 1957. Paris: Masson. Paper covered, 2200 fr.

IN this short book of 157 pages, the anatomy and technique of approach to calculi in the biliary tree are very completely studied and well illustrated both by fairly realistic diagrams and very good radiographs.

The instruments and technique of cholangiography during operation are well described, together with a short note on the radiological technique and apparatus.

There are photographs of pre-operative cholangiograms at once so fascinating and rare that one is tempted to suspect that the interpretations must in most cases have been arrived at after the operative findings, but this does not detract from their interest.

The surprising assertion is made, and backed by personal statistics, that calculi are more common in the left than in the right portion of the biliary tree.

Details of various techniques for the approach to stones fixed in the retropancreatic portion of the common bile-duct and of the ampulla are both interesting and instructive, and a special papillotomy forceps is illustrated.

Various methods of drainage of the biliary tree are described in some detail. The author is critical of the Kehr technique for drainage via the duodenum with a T-tube.

The book finishes with details of the technique of an operation that Mirrizi names "superior transduodenal choledoco-duodenostomy". This consists of passing a special curved forceps down through an incision in the common bile-duct about 2 cm. above the ampulla of Vater. The forceps are mounted with two fine points which are then pushed forward to pass through the sphincter of Oddi and can be felt through the anterior duodenal wall.

The duodenum is incised on to the forceps, which are then opened a little to stretch the sphincter. The opening so made is increased in size by a small incision between the points of the forceps and a special small de Pezzer type tube is grasped and pulled back so as to lie partly in the duodenum and partly in the common bile-duct.

This tube serves both as a temporary dilator and allows free passage of bile into the duodenum. The tube is fixed with fine catgut which is eliminated spontaneously after a few days.

For those interested in the technique of dealing with rare and dangerous obstructions in the biliary tree, this book is well worth the reading.

Anomalies of Intestinal Rotation and Fixation. By ROBERTO L. ESTRADA, B.Sc., M.D., C.M., D.Surg. (McGill), F.R.C.S.(C.), F.A.C.S., Demonstrator in Surgery, McGill University, Montreal, Canada. $9 \times 5\frac{3}{4}$ in. Pp. 161 + xx, with 39 illustrations. 1958. Springfield: Charles C. Thomas (Oxford: Blackwell Scientific Publications). 50s.

THE various irregularities which may occur in the intestinal tract due to intestinal rotation are always interesting to the surgeon who operates on the abdomen. Just after the First World War Dott put this subject on the map and put forward a classification. Mr. Estrada in his monograph puts forward a more up-to-date classification in which the term 'malrotation' has been discarded.

Quite a large portion of this volume deals with the clinical aspects of each anomaly of rotation and fixation. Modern X-ray examinations prove of real worth in the diagnosis of some of the anomalies.

The author, who has studied this subject from every angle, gives some sound advice to the reader regarding the surgical approach to these cases. The pre- and post-operative management and possible complications are well described. An excellent reference volume which surgeons will find most useful.

Textbook of British Surgery. Edited by Sir HENRY SOUTTAR, C.B.E., D.M.(Oxon.), F.R.C.S., Consulting Surgeon, London Hospital; and J. C. GOLIGHER, Ch.M.(Edin.), F.R.C.S.(Edin. and Eng.), Professor of Surgery, University of Leeds, and Surgeon, Leeds General Infirmary. Volume III. $9\frac{3}{4} \times 7$ in. Pp. 619 + viii, with 207 illustrations. 1958. London: William Heinemann. 105s.

WE have come to expect a high standard of this work, and Volume III has lived up to the reputation of the preceding volumes.

This volume covers genito-urinary surgery; peripheral vascular diseases; plastic surgery; actinomycosis; surgery of the tropics; venereal disease; radiology and radium therapy; surgery of the adrenal and parathyroid glands; blood transfusion; shock and chemotherapy.

The volume contains a wealth of information, is well balanced, and is profusely illustrated. Important surgical procedures are fully described and the basic viewpoint is essentially clinical and practical. The fifteen contributors are drawn from the leading medical schools and hospitals

throughout the United Kingdom and portray all the best in British surgery. This work will prove of real value to all who are studying for higher surgical examinations and degrees.

It is also an excellent reference book and we look forward with confidence and interest to the appearance of the fourth volume.

Eye Surgery. By H. B. STALLARD, M.B.E., M.A., M.D. (Cantab.), F.R.C.S.(Eng.), Hon. Ll.D.(St. Andrews), Surgeon, The Moorfields Eye Hospital; Eye Surgeon, St. Bartholomew's Hospital. Third edition, fully revised. $8\frac{3}{4} \times 5\frac{1}{2}$ in. Pp. 899 + xvi, with 671 illustrations. 1958. Bristol: John Wright & Sons Ltd. 95s.

THIS third edition of this great work on the surgery of the eye has been very thoroughly revised and brought up to date. Mr. Stallard has described the details of surgical operations on the eye which he considers have an accepted place in current practice.

The outstanding feature of the new edition is the excellence of the 275 new illustrations.

New material has been added on corneal transplants and the technique of various operations dealing with this new and important subject.

This new edition will take its place as the reference volume dealing with the surgery of the eye; it is a real credit to British surgical practice.

Year Book of Urology (1957–8 Series). Edited by WILLIAM WALLACE SCOTT, M.D., Ph.D., Director, James Buchanan Brady Urological Institute, The Johns Hopkins Hospital; Urologist-in-Charge, The Johns Hopkins Hospital; Professor of Urology, The Johns Hopkins University School of Medicine. $7\frac{3}{4} \times 5$ in. Pp. 359, with 79 illustrations. 1958. Chicago: The Year Book Publishers Inc. 57s.

IN his special introductory article the editor continues his studies on prostatic cancer started in the previous volume and gives news of a Prostate Study Group formed by the National Cancer Institute. We share his hope that some new steroid will be found which will prove to be the right one in the treatment of carcinoma of the prostate.

The remainder of the book contains abstracts from most of the extensive world literature on urological subjects. It is indispensable to the busy urologist who wishes to keep abreast of the times.

Medizin: Theorie und Klinik in Einzeldarstellungen. Vol. II. Die Angeborene Huftgelenksverrenkung und Ihre Behandlung. By GUSTAV HAUBERG, Head of Orthopædic University Clinic, Frankfurt. $9 \times 5\frac{3}{4}$ in. Pp. 142, with 58 illustrations. 1958. Heidelberg. D.M. 19.80.

THE problem of congenital dislocation of the hip is thoroughly reviewed in all its aspects in this, the second of a new series of monographs. The main thesis of the book is the novel role in treatment allotted to the shelf operation, based on a 10 years' follow-up study. Promoted from palliative adjunct to primary procedure, it is carried out immediately following accurate closed reduction of the dislocation, or to forestall dislocation in 'dysplastic' joints, at the earliest possible opportunity. Trauma in these often tiny infants is minimized by resort to a percutaneous technique, using autogenous heterografts.

While it may be argued that results are probably always favourably affected by early diagnosis whatever the mode of treatment, the early shelf operation is said to have a twofold rationale: bony development of both hypoplastic acetabulum and femoral head is encouraged; lengthy immobilization, reputed to lead to deformity of the femoral head, can be cut short without risking (re-) dislocation.

On the subject of open reduction, a conservative attitude is adopted. Advocated in the "exceptional case" on strictly clinical grounds, operative intervention is restricted where possible to an attack on interposing soft-tissue structures. The shelf operation is not advised here.

Format is handy, print clear, and the illustrations of uniformly good quality. The bibliography is extensive, so that it is possible to become familiar with the large continental literature, not usually quoted in English texts. The book is commended to the specialized reader.

Tracheotomy: a Clinical and Experimental Study. By THOMAS G. NELSON, Major, M.C., U.S.A.R. $10 \times 6\frac{1}{2}$ in. Pp. 111 + vi, with 47 illustrations. 1958. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox). 30s.

THIS is a reprint in book form of a 100-page article which appeared in three parts in the *American Surgeon* of last year. In the first chapter the author summarizes the purpose of the study under three headings: To present the story of the evolution of tracheotomy leading to its presently accepted position; to present an analysis of indications, technique, and complications in 310 operations, emphasizing certain lesser-known clinical uses; and to present a clinical and experimental evaluation of the technical aspects of the operation.

The second chapter is devoted entirely to the history of the operation from the earliest known to the present time. It is a compact résumé of the subject and makes an admirable introduction to the rest of the work.

The third chapter is the analytical study of 310 tracheotomies performed in the Brooke Army Hospital, Texas, which for study are grouped under three headings: (1) Cases with the mechanical ventilatory obstruction; (2) Cases with the secretory ventilatory obstruction; (3) Special uses of tracheotomy, such as to relieve pressure on the bronchial stump, as a route for endoscopy, for endotracheal anæsthesia, and for respiratory resuscitation.

A comparison is made of the various techniques employed and the various sites of the opening and a case is made for a transverse incision, division of the thyroid isthmus, and excision of a portion of the tracheal wall as a standard operation. No case is found for the division into high, medium, and low tracheotomy, but emphasis is laid on the need to make the opening high in cases needing mechanical respiratory assistance.

Complications and death occurring during and after the operation are discussed in an unusually frank manner and much useful information is extracted.

Emphasis is laid on the need for special skill in after-care and a useful outline of procedure is given, though more might be said about apnœa after tracheotomy.

The final chapter is on experiments carried out on dogs to determine the results of long-term healing after tracheotomy in various sites and using various cannulæ with special reference to the production of stenosis and the difference in intracranial and intrabronchial pressures resulting from an opening in the trachea.

The work as a whole is well written, pleasant to read, well documented, and contains much useful information. The concluding words, to the effect that this unique operation is likely to become more widely used, are undoubtedly true, and in producing this survey the author has performed service to both surgery and medicine.

It is not a book that one would keep for reference, but it should be read by surgeon and physician alike and so should be in the hospital library, and in this place it would be so much better if there were an index and the publishers were to grace its back with the title.

Anatomia dell'addome Operato. Con Appendice di Patologia. By L. SCHWARZ. 9¾ × 6½ in. Pp. 274, with 74 illustrations. 1957. Bologna: Cappelli Editore.

THE description of congenital abnormalities of form is an accepted part of the science of anatomy. The purpose of this book is to initiate a new branch of descriptive anatomy devoted to morphological changes due to surgical intervention within the abdomen. In the first chapter, a detailed system of topographical nomenclature is drawn up so that every portion of the gut and mesentery related to any kind of stoma or anastomosis may be separately referred to. Successive chapters then describe, for the most part with great completeness, the many types of anastomosis, resection, or external fistulization of the hollow organs practised from earliest to most recent times, including the use of isolated loops in œsophageal, gastric, and urological surgery. The solid viscera are less exhaustively treated; splenectomy and pancreatectomy are included, but not excision of parts of the liver. Operations on the nerves, veins, and arteries are also omitted, but there is an account of fixation operations. A final section describes some of the pathological consequences of the anatomical changes already recorded.

In most cases, the name of the originator is mentioned as each operation is described, but original papers are less evident in the bibliography, which generally cites secondary sources. Mis-spelled proper names include Dinnich, Lotheisen, and Taskner (Dinnick, Lotheissen, and Tasker), and there are unofficial abbreviations for the names of periodicals. There is no alphabetical index, but the table of contents is very detailed, headed "Index", and printed at the end.

The book is extremely well printed in Bodoni type on slightly glossy paper of excellent whiteness. The drawings are well reproduced, the layout is always pleasing, and every page has a clean, crisp appearance.

Year Book of Ear, Nose and Throat and Maxillofacial Surgery (1957–8 Series). Edited by JOHN R. LINDSAY, M.D., Professor and Head of the Section of Otolaryngology, The University of Chicago; DEAN M. LIERLE, M.D., Professor and Head of the Department of Otolaryngology and Maxillofacial Surgery, State University of Iowa College of Medicine; and WILLIAM C. HUFFMAN, M.D., Professor of Otolaryngology and Maxillofacial Surgery, State University of Iowa College of Medicine. 7⅝ × 5 in. Pp. 383, with 96 illustrations. 1958. Chicago: The Year Book Publishers Inc. 57s.

THIS new year-book contains a précis of all the important articles which have been published in 1957–8.

The antibiotic era has changed the face of the surgery of the ear, nose, and throat specialties; but, on the other hand, much new work has been developed. Decompression of the facial nerve, fenestration, mobilization of the stapes, and tympanoplasty are just a few of the new operative procedures which have been initiated.

Surgery has replaced radiotherapy in the treatment of cancer of the larynx, and as year passes year better results are being obtained.

For chronic derangement of the temporomandibular joint American surgeons appear to favour excision of the articular disk, while in Britain this operation is seldom performed because the dental surgeon is able to adjust malocclusion, which is the responsible agent for these conditions.

Many new plastic operations are now performed for cicatricial stenosis of the œsophagus and these are all described in this comprehensive year-book.

An excellent reference volume to modern literature in these subjects.

An Introduction to Experimental Surgical Studies. By W. J. DEMPSTER, F.R.C.S., Lecturer in Experimental Surgery, Postgraduate Medical School of London. 9 × 5½ in. Pp. 463, with 72 illustrations. 1957. Oxford: Blackwell Scientific Publications. 50s.

THE increasing scope of experimental surgery is rapidly leading to its evolution as a distinct branch of medical science. There are many surgical problems which can only be solved by experimental methods, yet the practising surgeon is not competent to pursue them without some special training in animal work. This book is not a laboratory manual, but it is a bridge between the clinic and the animal laboratory. Those who have particular problems can pick out the section in which they are interested and study what has already been done; those who are in search of unsolved problems can find them here in plenty, for many are posed. Rarely is the answer given, but a line of future work is always suggested. The text is stimulating but never dogmatic; the bibliography is extensive. Mr. Dempster advocates the appointment of full-time experimental surgeons, and after reading this book one must agree with him. If they will follow his lead in investigating problems which have a clinical application they will prove their worth.

Suspension Therapy in Rehabilitation. By MARGARET HOLLIS, M.C.S.P., Principal, School of Physiotherapy, Bradford Royal Infirmary; and MARGARET H. S. ROPER, M.C.S.P., Lecturer in Physiotherapy, University of Cape Town. With a Foreword by Sir ARTHUR PORRITT, K.C.M.G., K.C.V.O., C.B.E., M.A., M.Ch., F.R.C.S., Surgeon, St. Mary's Hospital, Paddington. 8½ × 5½ in. Pp. 220 + xii, with 112 illustrations. 1958. London: Baillière, Tindall & Cox. 25s.

REHABILITATION holds a very important place in the treatment of traumatic injuries and poliomyelitis cases. This essentially practical book stresses the importance of suspension therapy in the treatment of the ever-increasing volume of injuries, paraplegias, amputations, and rheumatic disorders.

Mrs. O. F. Guthrie Smith was the pioneer in this form of therapy, and this book is dedicated to her memory by two of her disciples who are the authors of this volume. Sir Arthur Porritt, who writes a foreword, has nothing but praise for this form of therapy.

The purpose of the book is to provide an up-to-date practical text-book for all who use suspensory therapy. The first part deals in detail with mechanical principles, techniques and methods of suspension, spring and pulley therapy, and the history of their development. The second part describes the clinical application of suspension, including geriatrics and disorders of the nervous system.

The book is well illustrated and should prove indispensable to all students of physiotherapy.

Medical Annual 1958. Edited by Sir HENRY TIDY, K.B.E., M.A., M.D. (Oxon.), F.R.C.P.; and R. MILNES WALKER, M.S. (Lond.), F.R.C.S., with the collaboration of 43 contributors. 8 3/16 × 5 1/16 in. Pp. 580 + xl, with 42 plates and 30 text illustrations. 1958. Bristol: John Wright and Sons Ltd. 42s.

THE *Medical Annual* for 1958 has undergone a change for the better, for instead of the articles being arranged in alphabetical order, the editors have arranged the "Review of the Year's Work" in sub-sections complete in themselves.

Four excellent and comprehensive special articles are included, one on intersexuality by Dr. P. M. F. Bishop, a second on wound infection in operation theatres by

Dr. Robert Blowers, a third by Dr. J. H. Middlemiss on the dangers arising from the medical use of X rays, and a fourth by Dr. Wilfrid Sheldon on the changing emphasis in pædiatrics. These four articles in themselves are most valuable and give the reader a remarkable insight into these important problems.

The surgeon cannot help but be interested in this *Medical Annual* because Professor Milnes Walker has skilfully incorporated all that is new in surgery and anæsthesia. Induced hypotension and the muscle relaxants are well described by Dr. Langton Hewer, while Mr. Kent Harrison gives an admirable account of intracardiac surgery together with an excellent description of the various pump oxygenators.

The whole volume is full of interesting surgical articles.

We notice that this is the last year the Senior Editor, Sir Henry Tidy, will function in that capacity, and we wish him every success in his retirement. He will at least have the great satisfaction of knowing that this year the *Medical Annual* has surpassed earlier volumes in value and utility. The *Medical Annual* to-day is one of the important books of the year.

Orr's Operations of General Surgery. By GEORGE A. HIGGINS, M.D., F.A.C.S., Associate Professor of Surgery, University of Kansas School of Medicine; and THOMAS G. ORR, jun., M.D., F.A.C.S., Associate in Surgery, University of Kansas School of Medicine. Third edition. 10 × 7 in. Pp. 1016 + vi, with 835 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 140s.

IT is nearly ten years since the second edition of this large comprehensive work appeared and much has happened in that time. We regret that the former author whose name was associated with this work has died, and the third edition has been edited by Professor Higgins and Dr. Orr's son, Thomas G. Orr. The layout of the new volume remains much the same as earlier editions, but many new illustrations have appeared. As one would expect, much of the new material in this third edition concerns certain special fields of surgery, such as thoracic and cardiovascular surgery, and these new sections have been very well presented and illustrated.

This work is devoted to operations of general surgery, yet quite a proportion of its pages are devoted to orthopædic and gynæcological operations. Perhaps the authors consider that both these branches of surgery come under the surgical umbrella of general surgery. There can be little doubt that the general surgeon may at any time be required to amputate a limb, set a fracture, or remove a uterine fibroid, and therefore it is pleasing to find a book on operative procedure which includes all these subjects.

This work is well balanced and presents the present surgical operative techniques which are in vogue in America.

L'Auto-intoxication après Brûlure. By T. GODFRAIND. 9¼ × 6¼ in. Pp. 191, with 49 illustrations. 1958. Bruxelles: Editions Arscia. 250 fr. belg.

THE concept of 'primary toxæmia' due to a specific toxic substance elaborated by burned tissue is no longer very popular, since recent work has shown that many of the clinical signs and symptoms in the early post-burn period are in fact due to uncorrected oligæmic shock or early bacterial infection. Nevertheless, several workers have isolated toxic substances from burned tissue and this work, started at Louvain in 1940, establishes the toxicity of certain polypeptides and peptones in experimental burns in frogs and rabbits. A great increase in the activity of proteases in burned tissue was observed and a toxic factor was traced in the euglobulin fraction of the plasma and œdema fluid. This toxic factor was found capable of producing severe shock and even death after subcutaneous and intravenous injection in animals. The pathological changes were found to be indistinguishable from those found in extensive burns. The author has not yet extended his investigation to the detailed study of burned tissue in man.

The monograph is beautifully presented and the bibliography lists several papers which are not widely known in this country and which merit close study. A rather surprising omission is the absence of any references to the work carried out in Sheffield by Professor H. N. Green and his colleagues.

Traumatologie Infantile. By P. L. CHIGOT and P. ESTÈVE. 10⅝ × 6 in. Pp. 357, with 114 illustrations. 1958. Paris: Expansion Scientific Française. 5000 fr.

THIS book is based on the authors' combined experience of the injuries sustained by some 6600 children admitted to a surgical unit in Paris over a 5-year period. Of these some 4000 were fractures, 2000 head injuries, and the remainder burns (500), abdominal injuries (20), and soft-tissue wounds (100).

Despite the imposing binding, the clear type on highly glazed paper, and the novel technique used for the diagrammatic illustration of fractures, this book is disappointing, for it is not clear for whom it is intended. It is certainly not a student's text-book, nor can it be classified as a text-book of pædiatric traumatic surgery, since it gives very little detailed guidance on surgical techniques and practice. Rather does the volume appear to fall into the category of a 'Five-year Hospital Report'.

The general principles of treatment conform to accepted British practice. It was surprising to find that in some 66 pages on fractures of the lower limb only one very sketchy paragraph was devoted to the torsion-avulsion injury so commonly seen after 'run-over' traffic accidents. There is very little space devoted to the problems of blood transfusion and resuscitation in infants, or to the very large amounts of blood that may be lost during certain operations. The chapter on burns, in particular, only deals with oligæmic shock in very general terms.

The most satisfying chapters are those dealing with head injuries and the medico-legal aspects of childhood injuries. In the latter, the authors plead for reasonable delay before giving a final medical report for the assessment of civil damages. Head injuries, in particular, may have disastrous sequelæ which are not immediately apparent, and an unduly optimistic early report can be a serious handicap in later claims for damages. Conversely, opinions expressed soon after major limb injuries may be unduly pessimistic and indirectly affect the child's education and training.

The bibliography at the end of the book is sadly incomplete. The names of many authors, mentioned repeatedly in the text, cannot be found in the index, and there are several serious errors of spelling of the names of surgeons well known both here and on the Continent.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Lehrbuch der Chirurgie. Edited by H. HELLNER, R. NISSEN, and K. VOSSSCHULTE. 10 × 6¾ in. Pp. 1112 + xxxvi, with 652 illustrations. 1958. Stuttgart: Georg Thieme. D.M. 84.

Leistungen und Ergebnisse der Neuzeitlichen Chirurgie. By EMIL K. FREY. 10½ × 7¼ in. Pp. 339 + xii, with 154 illustrations. 1958. Stuttgart: Georg Thieme Verlag. D.M. 84.

Human Blood in New York City. A study of its procurement, distribution and utilization, conducted by the Committee of Public Health, The New York Academy of Medicine. 8½ × 5½ in. Pp. 147. 1958. New York: New York Academy of Medicine.

Actualités Médico-chirurgicales. Obliterations Arterielles (Membres inferieurs); Thérapeutique des Prolapsus Genitaux; Recto-colite Muco-hémorragique. By R. FONTAINE, G. CORDIER, A. BUSSON, and J. MIALARET. 8½ × 6½ in. Pp. 188, with 40 illustrations. 1958. Paris: Masson. 2000 fr.

The Collected Papers of Hugh Trumble. Edited by LEONARD COX, M.D.; R. S. LAWSON, F.R.C.S.; and T. E. LOWE, M.D. 8¾ × 5½ in. Pp. 302 + xxiv, fully illustrated. 1957. Melbourne: Melbourne University Press (1958. London: Cambridge University Press). 84s.

The Physical Treatment of Varicose Ulcers. A Practical Manual for the Physiotherapist and Nurse. By ROWDEN FOOTE, F.I.C.S., M.R.C.S., L.R.C.P., D.R.C.O.G., Surgeon-in-charge, Varicose Vein Clinic, Harrow Hospital. 7¼ × 4¾ in. Pp. 125 + xii, with 88 illustrations. 1958. Edinburgh: E. & S. Livingstone Ltd. 15s.

Surgery and Surgical Nursing. By EDWARD S. STAFFORD, B.A., M.D., F.A.C.S., Associate Professor of Surgery, The Johns Hopkins University; and DORIS DILLER, B.A., M.A., R.N., Associate Professor of Nursing, Skidmore College. Third edition. 9¼ × 6 in. Pp. 469 + viii, with 174 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. Ltd. 35s.

Anaesthesia Abstracts. By JOHN S. LUNDY and FLORENCE A. MCQUILLEN. Vol. XLVII. 10¼ × 8 in. Pp. 259. 1958. Minneapolis: Burgess Publishing Co. (London: The Mayflower Publishing Co. Ltd.). 28s.

Notes de Techniques Chirurgicales de 'La Presse Médicale'. Collected by LUCIEN LEGER. 9½ × 6½ in. Pp. 313 + viii, with 209 illustrations. 1958. Paris: Masson et Cie. 3800 fr.

Atlas of Tumor Pathology. Section VII, Fascicle 25: **Tumors of the Liver and Intrahepatic Bile Ducts.** By HUGH A. EDMONDSON, M.D., Professor of Pathology, University of Southern California, School of Medicine, Los Angeles. 10¼ × 7$\frac{9}{16}$ in. Pp. 216, with 207 illustrations. 1958. Washington: Armed Forces Institute of Pathology. $2.25.

Atlas of Tumor Pathology. Section V, Fascicle 20: **Tumors of the Esophagus.** By ARTHUR PURDY STOUT, M.D.; and RAFFAELE LATTES, M.D. 10¼ × 7$\frac{9}{16}$ in. Pp. 105, with 58 illustrations. 1957. Washington: Armed Forces Institute of Pathology. $1.00.

Intracardiac Phenomena. By ALDO A. LUISADA, M.D., Director, Division of Cardiology and Associate Professor of Medicine, The Chicago Medical School; and CHI KONG LIU, M.D., Chief, Laboratory of Catheterization and Associate of Clinical Medicine, The Chicago Medical School. Second edition. 10 × 6¾ in. Pp. 179 + x, with 82 illustrations. 1958. New York and London: Grune and Stratton, Inc. $9.50.

Orthopædics in General Practice. By W. H. GERVIS, M.A., M.B., B.Ch. (Cantab.), F.R.C.S., Orthopædic Surgeon, West Kent Hospital, Maidstone, Kent. 7¼ × 4¾ in. Pp. 120, with 32 illustrations. 1958. London: William Heinemann. 10s. 6d.

Callander's Surgical Anatomy. By BARRY J. ANSON, M.A., Ph.D. (Med. Sc.), Chairman, Department of Anatomy, and Robert Laughlin Rea Professor, Northwestern University Medical School and Member of Staff, Passavant Memorial Hospital; and WALTER G. MADDOCK, M.S., M.D., F.A.C.S., Edward S. Elcock Professor of Surgery, Northwestern University Medical School. Fourth edition. 10 × 7 in. Pp. 1157 + xviii, with 1047 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 147s.

Textbook of Surgery. Edited by GUY BLACKBURN and REX LAURIE. Pp. 1122, fully illustrated. 1958. Oxford: Blackwell Scientific Publications. 84s.

CORRIGENDA

D. N. Baron, K. J. Gurling, and E. J. Radley Smith: "The Effect of Hypophysectomy in Advanced Carcinoma of the Breast", 1958, Vol. XLV, No. 194, p. 593.

In *Table V*, p. 595, the total cortisone dosage at day-minus-one in patients with normal adrenal function should be 100 mg.

C. Q. Henriques: "Osteomyelitis as a Complication in Urology", 1958, Vol. XLVI, No. 195, p. 19.

In the caption to *Fig. 22 for* Berschet's *read* Breschet's.

On p. 27, Discussion, paragraph 5, *for Case* 3 shows only a spinal lesion *read Case* 3 shows not only a spinal lesion.

ADDENDUM

Peter Ryan: "Emergency Resection and Anastomosis for Perforated Sigmoid Diverticulitis", 1958, Vol. XLV, No. 194, p. 611.

The author wishes to acknowledge the generous assistance of Dr. E. M. Stirk, Pathologist, Leicester General Hospital, who prepared and photographed the specimens described.